ICER Psoriasis feedback on draft evidence report published September 29,2016

Below is our feedback and commentary on the draft evidence report for psoriasis:

Insufficient penalty for non-responders:

- As we have stated in our previous feedback there does not appear to be a sufficient penalty for patients who do not respond. Based on previous literature and HTA submissions, a proportion of psoriasis patients who do not respond experience hospitalization (Stern 2003, Woolacott 2006). As a result, apremilast has one of the lowest incremental costs per QALY despite having by-far the lowest efficacy. We asked that you explore including the NICE methodology where hospitalization costs were included in the model estimates.

Dsocontinuation rate for TIMs:

- The annual discontinuation rate of 20% (while used in previous NICE submissions) in your previous model was changed to assume a 30% discontinuation for Humira, Enbrel and Remicaid and 16% for IL-17s and Stelara. No discontinuation rate was provided for Otezla. The study you citeds for the discontinuation rate for ustekinumab only included 195 patients and is not reflective of real world practice. We recommend having similar discontinuation rates for all products and performing a sensitivity analysis using 10% discontinuation rates.

Clarity around real world utilization and patient mix of 45/90 mg arms of ustekinumab:

- We were unclear as to how ustekinumab 45/90 mg was combined into a single treatment (when almost all studies have separate 45mg and 90mg arms), and whether ustekinumab was administered according to weight-based dosing. It looks like this was partially addressed in your cost calulations but it is still unclear in the model how this impacted efficacy calculations. It does not appear that they use lower weight patients randomized to 45mg and higher weight patients randomized to 90mg.

Differences in the methods used to calculate the PASI response rates from trials

- ITT-NRI and ITT-LOCF data reporting are used inconsistently when both reporting methods are available.
    - a. Menter 2008 (REVEAL) uses ITT-NRI
    - b. Papp 2015 (ESTEEM) uses ITT-LOCF
    - c. Paul 2015 (ESTEEM 2) uses ITT-LOCF

Also there was lack of transperancy on the source of the data for PASI-50. It would be nice to know where you got the data from and how it was validated.

AIMED ALLIANCE
Alliance for the Adoption of Innovations in Medicine

October 20, 2016

Steven Pearson, MD
Institute for Clinical and Economic Review
2 Liberty Square, Ninth Floor
Boston, MA 02109

Dear Dr. Pearson:

The Alliance for the Adoption of Innovations in Medicine (Aimed Alliance) is a tax-exempt, not-for-profit organization that improves health care in the United States by expanding access to evidence-based treatments and technologies. On behalf of Aimed Alliance, I respectfully submit the following comment in response to the Draft Evidence Report, entitled "Targeted Immunomodulators for the Treatment of Moderate-to-Severe Plaque Psoriasis" ("Draft Report") published by the Institute for Clinical and Economic Review ("ICER").

Psoriasis is a significant public health problem that affects approximately 7.5 million adults in the United States.[1] It is a chronic inflammatory disease of the immune system that mostly affects the skin and joints.[2] Plaque psoriasis is the most common type of psoriasis, affecting up to 80 percent of individuals with psoriasis.[3] Psoriasis can dramatically impact individuals' quality of life and self-esteem, and can result in depression, social isolation, and work-related problems.[4] Individuals with psoriasis must have access to effective treatment options. Yet, we fear that the Draft Report will limit those options.

QALYs are Discriminatory

The use of quality-adjusted life-years ("QALYs") is inconsistent with American values and public policy. Recognizing that value-based frameworks can result in an inappropriate rationing of care, Congress added language to the Patient Protection and Affordable Care Act that prohibited the Patient-Centered Outcomes Research Institute ("PCORI") from using QALYs as a threshold for determining coverage, reimbursement, or incentives in the Medicare program. The ban reflected a long-standing concern in the U.S. that the approach would lead to discrimination on the basis of age and health status, unfairly favoring younger and healthier populations.

QALYs put a price tag on the value of a human life that merely reflects the individual's diagnosis and deems those with chronic, debilitating, and rare conditions, such as psoriasis, as

[1] Charles G. Helmick, *Prevalence of Psoriasis Among Adults in the U.S.*, 47(1) Am J. Prev. Med. 27 (2014); *Psoriasis Treatments and Drugs*, Mayo Clinic, http://www.mayoclinic.org/diseases-conditions/psoriasis/basics/treatment/con-20030838 (last visited Oct. 20, 2016).
[2] *Psoriasis*, American Academy of Dermatology, https://www.aad.org/media/stats/conditions/psoriasis (Oct. 20, 2016).
[3] Ann Pietrangelo, *Psoriasis by the Numbers: Facts, Statistics, and You*, Health Nice (June 9, 2016), http://www.healthline.com/health/psoriasis/facts-statistics-infographic#Introduction1.
[4] Loretta Fala, *Otezla (Apremilast), an Oral PDE-4 Inhibitor, Receives FDA Approval for the Treatment of Patients with Active Psoriatic Arthritis and Plaque Psoriasis*, 8 Am Health Drug Benefit 105 (2015).

being worth less than the rest of the population. They treat individuals' lives and health as a commodity and ignore the patients' and practitioners' individualized concept of the value of treatment. Therefore, the QALY should not be used to set a threshold for a large population of individuals with one-of-a-kind life narratives across a complicated health care system.

Prioritizing Access to Options

To ensure patients receive adequate care, quality and choice of treatment options should not, by default, be sacrificed for cost-saving measures. The United States Court of Appeals for the Ninth Circuit has stated that "[f]aced with such a conflict between financial concerns and human suffering . . . the balance of hardships tips decidedly in [the patients'] favor."[5] Yet, the Draft Report concludes that targeted agents other than infliximab do not represent good economic value unless drug rebates and work productivity impacts are assessed, in which case they are moderately cost effective. It also concludes that "if second-line targeted drug use is high, . . . the main means of discrimination among agents should be price."

These conclusions ignore several benefits that immunomodulators provide in improving the quality of life of patients and controlling their symptoms. They also ignore that individual patient response, relevant comorbidities, and patient preference must also be considered when determining a treatment's value.[6]

As ICER acknowledges, individuals with psoriasis have unique responses to different psoriasis medications. Individuals with psoriasis may build up a resistance to various medication over time.[7] Their medication may become ineffective, and therefore, they must have access to all treatments available to them. Therefore, the value of each of these drugs must be made at the patient level, on a case-by-case basis given that each individual responds to these treatments differently.

Patient and Practitioner Perspectives

Patients must have a meaningful role in the discussion of value. They are directly impacted by a report that seeks to define the effectiveness and value of their treatment options. Therefore, accounting for how patients define the value of their treatment options should be critical to ICER's analysis.

Although ICER consulted with patients and patient groups on the topic of moderate-to-severe plaque psoriasis, it does not appear that ICER incorporated patient feedback. For example, the Draft Report states that patient groups discussed benefits that were not captured in clinical trials, such as reductions in distress and anxiety. Psoriasis tends to affect overall emotional wellbeing in 88 percent of patients, and interferes with the enjoyment of life in 82 percent.[8] It can result in

[5] Lopez v. Heckler, 713 F.2d 1432, 1437 (9th Cir. 1983).
[6] A. Schieder, et al., *Comorbidities Significantly Impact Patients' Preferences for Psoriasis Treatments*, 67 J. Am Acad. Dermatol. 363 (2012).
[7] *Psoriasis Treatments and Drugs*, Mayo Clinic, http://www.mayoclinic.org/diseases-conditions/psoriasis/basics/treatment/con-20030838 (last visited Oct. 20, 2016).
[8] April W. Armstrong, et al., *Quality of Life and Work Productivity Impairment among Psoriasis Patients: Findings from the National Psoriasis Foundation Survey Data 2003-2011*, 7(12) PLos One 2012.

anger, frustration, helplessness, embarrassment, and self-consciousness in a large majority of patients. While ICER did take into consideration the significant impact psoriasis has on work productivity, it appears that ICER did not take emotional and psychological impacts into consideration in its value assessment.

Additionally, the opinions of health care practitioners are vital in understanding the value of treatment options. Over the course of professional practice, health care practitioners obtain clinical experience with medications and identify emerging clinical trends and best practices. They can employ their practical knowledge to determine which medications are best suited to each patient's individual needs. However, it does not appear that ICER consulted with any dermatologists, internal medicine physicians, rheumatologists, or other physicians who commonly treat moderate-to-severe plaque psoriasis.

Nonmedical Switching

As ICER acknowledges, insurers and pharmacy benefit managers often employ burdensome benefit utilization management tools, such as step therapy and prior authorization to limit access to immunomodulators. Another commonly employed policy to reduce access to immunomodulators is nonmedical switching. Nonmedical switching occurs when an insurer requires a stable patient to switch from his or her current, effective medication to a cheaper, alternative drug.[9] The change occurs as the result of the insurer dropping a medication from the formulary altogether, moving a drug to a higher cost tier, or increasing the out-of-pocket costs owed after the plan year has begun. Nonmedical switching is done without consideration of the medical repercussions or reasoning behind the prescriber's selection of the original medication, and often without the prescriber's knowledge.[10]

This practice is particularly problematic for immunomodulators because, as previously discussed, patients can build up an immunity or tolerance to their medication. Therefore, if a stable patient is switched to a different treatment in an effort to save money, and that cheaper treatment is less effective, it is possible that switching back to their original medication will no longer be effective. Therefore, we caution against using assessments based on cost-savings alone, especially for stable patients.

Conclusion

Thank you for your consideration regarding the Draft Report, and we are available for discussion to address our shared goals of access to high quality health care at a price that accurately reflects public and personal benefits in the Final Report.

Respectfully submitted.

Stacey L. Worthy
Executive Director

[9] *Keeping Stable Patients on Their Medications*, Coal. of State Rheumatology Organizations, http://www.csro.info/Switching (last visited Jan. 14, 2016).
[10] *Id.*

Amgen Response to ICER Draft Evidence Report for Moderate-to-Severe Plaque Psoriasis

Amgen is a science-based company committed to developing and delivering innovative medicines. Our mission is to serve patients. We appreciate the opportunity to comment on the ICER Draft Report "Targeted Immunomodulators for the Treatment of Moderate-to-Severe Plaque Psoriasis: Effectiveness and Value."

Moderate-to-severe plaque psoriasis (PsO) is a chronic, systemic inflammatory disease associated with widespread skin involvement, significant comorbidities, and crippling physical, economic, emotional, and social consequences that accumulate over the course of a patient's life.[1] Systemic biologic treatments are often the only effective option for patients with this hard-to-treat disease.[2] Biologic PsO treatments have transformed the outcome of this disease in life-altering ways that short-term trials fail to capture.

While we disagree with ICER's use of cost-effectiveness thresholds and inadequate one-size-fits-all modeling methods, the findings described within the ICER Draft Report clearly demonstrate that all biologic PsO treatments, including Enbrel® (etanercept), are good value. All targeted therapies largely fall within ICER's willingness-to-pay threshold of $100K to $150K per quality adjusted life year (QALY), and all were well under the $150K/QALY threshold after a 20% discount (a closer approximation of some products' true market price). The demonstrated value of all biologics for PsO reinforces the importance of preserving treatment choice for the patient as specific disease characteristics, clinical expertise/judgement, and patient preferences affect treatment choice.

After a careful review of the ICER Draft Report, we found the following issues warrant attention:

- The analysis lacks transparency and is difficult to interpret; the studies and study arms included in the NMA for determination of Psoriasis Area and Severity Index (PASI) responses for each product need to be explicitly identified with a clearly defined selection process.
- The phase 3b LIBERATE study comparisons between apremilast and etanercept are based on an unpublished noncomparative design and should not be used as a direct comparison for determining clinical equivalency.
- Model inputs for nontargeted agents should be based on current practice patterns and costs; ICER's use of 2003 data is inappropriate when current data are available and biases the analyses against targeted biologics.
- A wholesale acquisition cost (WAC) price with a single across-the-board discount does not reflect true patient and payer costs associated with PsO treatments; alternative price sources, such as Average Sales Price (ASP), should be used in the primary analysis.
- Administrative costs need to be corrected to reflect that typically only the first dose of self-administered products, such as etanercept, is administered in an office setting.
- The uncertainty in PASI measures limits any justifiable differentiation in value among biologics; hence, the Draft Report should value the biologics similarly.
- Psoriatic arthritis (PsA) is a significant joint and skin comorbidity in patients with moderate-to-severe PsO that needs to be incorporated into ICER's analysis and model.
- Patient-centric outcomes, such as long-term benefits of targeted treatments, should be integrated into the economic analysis.

The analysis lacks transparency and is difficult to interpret; the studies and study arms included in the NMA for determination of PASI responses for each product need to be explicitly identified with a clearly defined selection process.

ICER should clarify trial inclusion criteria, including how the NMA studies were selected for inclusion and how between-trial heterogeneity was accounted for. Additional details regarding how QALYs were derived from PASI efficacy inputs are also needed.

The cornerstone of the model's comparative clinical effectiveness and value sections is the NMA of PASI response. The NMA methods should clearly state and provide references for the studies selected and include an assessment of effect-modifiers that is in line with accepted guidelines.[3,4]

An assessment of the studies in the NMA and their fit with the analysis population should be included in the report. The NMA methods described in Appendix G in the Draft Report are unclear and fail to provide information on the rationale for the studies selected to derive PASI responses. To have valid treatment-effect estimates, the individual studies included in the NMA need to align with the population of interest for which the cost-effectiveness analysis is performed. It is unclear which randomized controlled trials (RCTs) were included in specific analyses and why only some of the treatment regimens from the RCTs were selected. In attempting to identify etanercept studies, Table 4 of the Draft Report lists 7 key trials for etanercept (p28), whereas, up to 12 trials with etanercept are identified elsewhere in the Draft Report. It is challenging to evaluate results of the NMA without specific references and clear methods.

Transparency in the cost modeling is necessary to enable proper evaluation of the cost-effectiveness model and the life-altering benefits derived from targeted PsO treatments. There was no transparent assessment of whether the trials in the NMA are sufficiently similar regarding effect-modifiers (e.g., distribution of prior biologic use or baseline PASI) or timing of endpoint assessments. This information is essential to determine whether the estimate of treatment effects generated by the NMA are sufficiently robust to be used in the cost-effectiveness model and to ensure clinically plausible and interpretable incremental cost-effectiveness ratios.

The Phase 3b LIBERATE study comparisons between apremilast and etanercept are based on an unpublished noncomparative design and should not be used as a direct comparison for determining clinical equivalency

The report includes a LIBERATE study comparison between apremilast and etanercept that is flawed and should not be included in this analysis. Fundamentally, this study has a noncomparative design and was not powered to compare apremilast and etanercept.[5,6] Notably, the etanercept dose used in the LIBERATE study was not the labeled starting dose. Instead, the study used the etanercept 50 mg weekly maintenance dose, which biases the comparison.

The ICER Draft Report makes eight different comparative statements between etanercept and apremilast using the LIBERATE study, including almost 20% of the Comparative Clinical Effectiveness Summary section. This section, intended to describe "head-to-head" studies, states the evidence is judged insufficient between etanercept and apremilast.[7] Despite this acknowledgement, the section includes a long discussion of this study and indirect evidence between apremilast and etanercept before concluding that the products are "functionally equivalent for all other comparisons." The "equivalence" of apremilast and etanercept is based on

two highly tenuous statements in the Comparative Clinical Effectiveness Summary: (1) the conclusion of "no statistically-significant difference" based on a post hoc analysis of the poorly designed LIBERATE study and (2) that "both agents are consistently ranked together in the network meta-analysis" despite a statistical difference between apremilast and etanercept in the ICER NMA. In making the second statement, ICER undermines not only the NMA evidence that suggests differences exist between apremilast and appropriately-dosed etanercept, but also the entire NMA.

Given these issues and others detailed in Appendix A of this response, Amgen requests that this study and comparative claims be removed from the ICER Draft Report and any analyses including these data be rerun. Amgen also requests the deletion of Voting Question 5 "Is the evidence adequate to demonstrate that apremilast provides equivalent or greater net health benefit than etanercept?" as Question 6 adequately captures this query.

Model inputs for nontargeted agents should be based on current practice patterns and costs; ICER's use of 2003 data is inappropriate when current data are available and biases the analyses against targeted biologics.

The nontargeted therapy regimens and their costs are described vaguely in the Comparative Value section of the Draft Report. The acquisition costs provided are most likely a low estimate of their true costs;[8] the nontargeted therapy regimen costs should represent current US practice in patients with moderate to severe PsO. The current nontargeted therapies available to patients include multiple oral immunomodulators, systemic retinoids, phototherapy with and without chemotherapy, and a range of topical treatments with several different mechanisms of action. Some of these therapies have recently been made available to patients as novel agents or improved dosage forms. The nontargeted therapy and costs description is from a 2003 database analysis,[9] and does not include these newer therapies and dosage forms. This analysis also notes the limitation of not capturing all costs involved with these treatments, which would underestimate the total cost of this intervention that serves as the primary comparator for the cost-effectiveness analysis.

Additionally, the cost of the nontargeted therapy is based on a price from the pre-biologic practice era in 2003, inflated to 2016 costs using inflation factors that were not included in the report. While the nontargeted therapy sensitivity analysis of the cost-effectiveness results attempts to address the low costs and outdated data, the large variation in results of the sensitivity analysis suggests the need for a more accurate portrayal and costing of these treatments based on today's standards. ICER needs to use updated nontargeted therapy costs based on true 2016 utilization and costs. ICER should survey databases, practitioners, and patients to best determine the prescribed therapies that are acceptable to patients with moderate to severe PsO. These treatments should be acceptable for use by patients over the 10-year time horizon since the nontargeted therapy arm assumes a benefit over this period. After establishing the new nontargeted therapy regimen, its cost should be derived to represent an accurate value comparison.

The wholesale acquisition cost (WAC) prices with a single across-the-board discount does not reflect true patient and payer costs associated with PsO treatments; alternative price sources, such as Average Sales Price (ASP), should be used in the primary analysis.

The use of discounted drug costs would significantly improve the accuracy of the cost-effectiveness model. Given that the discounted cost represents a closer approximation of some targeted PsO agents' true market price, it should be the primary economic analysis. The WAC is just one data point in the discussion of price and should be as up-to-date as possible before discounts are applied. While WAC is the list price to wholesalers, usually wholesalers and other purchasers of drugs (such as pharmacies, hospitals, payers, and physician groups) negotiate considerable discounts and rebates for the products they purchase. These discounts and rebates drive down drug prices and are not reflected in the WAC. The publicly available ASP used in Medicare Part B is one source that can be used to estimate the drug discounts.[10] For example, the ASP of etanercept is 74.5% of the WAC. With discounts varying across drugs, applying a single discount rate does not accurately reflect prices paid in the U.S. ICER should seek to understand the differences in price discounting and refine the price discounts to achieve accurate prices for each drug.

The economic analysis has a 10-year time horizon, but only accounts for the time discounting of costs. During this time horizon and over a product lifecycle, drug prices are dynamic. The price at a single point in time only answers a static question of value today. A good economic evaluation of a product would understand the value across time from launch of a product through biosimilar entry to full replacement by more efficacious treatment options. The economic model, at a minimum, needs to include the entry of biosimilars in the market and use appropriate costs in those years. ICER should anticipate the changing treatment costs and incorporate them into the model to more appropriately value these interventions.

Administrative costs need to be corrected to reflect that typically only the first dose of self-administered products, such as etanercept, is administered in an office setting.

ICER makes a series of assumptions around biologic administration that are inconsistent with common practice. The Enbrel U.S. Prescribing Information instructs that the first injection should be performed under the supervision of a qualified healthcare professional. Patients rarely return to the office for repeat injections and generally self-administer etanercept utilizing the product's Instructions For Use; educational material and services are also provided by the manufacturer to help with self-administered injections (i.e. the Amgen Enbrel Support™ Nurse Partners™ program). Because dermatologists rarely administer injections to patients, the assumption that all injections during the induction period occur in the office is inappropriate for etanercept. Amgen recommends adjusting the assumption from all etanercept-induction injections performed in the office to one etanercept injection performed in the office.

The uncertainty in PASI measures limits any justifiable differentiation in value among biologics; hence, the Draft Report should value the biologics similarly.

Given the complexity of psoriatic disease, we appreciate ICER's statement[11] that "This uncertainty hinders our understanding of the relative effectiveness of these agents." Uncertainty is seen predominantly in the PASI measurements, especially when body surface area (BSA) involvement is low; PASI is a relatively insensitive measure in patients with low BSA involvement. Also, patients can often achieve satisfactory responses based on their signs and

symptoms that are not adequately captured by PASI scores. As a result, use of PASI scores translated into utilities further expands the uncertainty. Additional examples of uncertainty in the costs were noted previously with market-based drug costs and administration fees. While the sensitivity analysis attempts to explain some of the uncertainty, it suggests that these biologics are similarly valued. The report should acknowledge the uncertainty and conclude these drugs have similarly good value and are cost effective.

PsA is a significant joint and skin comorbidity in patients with moderate-to-severe PsO that needs to be incorporated into ICER's PsO analysis and model.

ICER missed a significant opportunity by not addressing PsA, a common PsO comorbidity that affects up to 30% of patients with moderate to severe PsO. In patients with both PsO and PsA, up to $2184 additional costs are incurred annually.[12] PsA can contribute to differential effects on QALYs and costs as the targeted therapies have variable effectiveness for treating PsA. Given these differences and the high prevalence of PsA in patients with PsO, PsA as a comorbidity should be included in the ICER PsO analysis.

Patient-centric outcomes, such as long-term benefits of targeted treatments, should be integrated into the economic analysis

The report qualitatively addresses key patient issues unique to moderate-to-severe PsO in Section 2.4: Insights Gained from Discussions with Patients and Patient Groups of the Draft Report. The economic analysis should quantify these insights and the treatment benefits of avoiding the long-term cumulative economic, emotional, and social consequences of PsO. Short-term PsO clinical trials capture neither these cumulative life impairments nor the long-term benefits of therapeutic interventions. In order to represent the long-term PsO patient experience identified in the report in the economic model, ICER should integrate these concepts into the model and further show the value of these lifelong therapies beyond the standard clinical trial time horizon in its cost-effectiveness analysis.

As patients can often also achieve satisfactory responses based on their signs and symptoms that are not adequately captured by PASI scores, ICER should consider adjusting short-term trial-based utility with a long-term patient-based utility augmentation factor to test what omitting longer-term outcomes means for the base model. For example, one could report in a sensitivity analysis the costs per QALY where the long-term utility was 20%, 40% or even 50% higher in long-term use than that captured in short-term trial metrics.

Conclusion

The ICER Draft Report demonstrates good value at market prices for all PsO treatments in this analysis despite using the one-size-fits-all economic model that relies too heavily on short-term studies and lacks patient-specific impacts. ICER has a responsibility to provide the evidence, costs, and patient perspective in their NMA in a highly transparent and credible manner. Development of a proper economic model that accounts for the significant physically and emotionally life-altering patient factors associated with PsO and reflects U.S. culture and practice patterns would best represent the value of PsO treatments in the U.S. Despite these limitations, the ICER analysis reinforces the importance of preserving patient treatment choice across all PsO treatments based on specific disease characteristics, clinical expertise and judgement, and patient preference.

References

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7. ICER. Draft Report: Targeted Immunomodulators for the Treatment of Moderate-to-Severe Plaque Psoriasis: Effectiveness and Value. See I* in Table 12 (p. 48).
8. ICER. Draft Report: Targeted Immunomodulators for the Treatment of Moderate-to-Severe Plaque Psoriasis: Effectiveness and Value. See Table 14: Drug acquisition costs (p. 53)
9. Yu AP, Tang J, Xie J, et al. Economic burden of psoriasis compared to the general population and stratified by disease severity. *Curr Med Res Opin.* 2009;25(10):2429-2438.
10. CMS. Centers for Medicare & Medicaid Services. Medicare Part B Drug Average Sales Price. 2016 ASP Drug Pricing Files. Available at: https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/2016ASPFiles.html. 2016.
11. ICER. Draft Report: Targeted Immunomodulators for the Treatment of Moderate-to-Severe Plaque Psoriasis: Effectiveness and Value. See p. 46
12. Kimball AB, Guerin A, Tsaneva M, et al. Economic burden of comorbidities in patients with psoriasis is substantial. *J Eur Acad Dermatol Venereol.* 2011;25(2):157-163.

Appendix A

ICER should eliminate or significantly reduce the extensive assessment of the LIBERATE study comparing apremilast and etanercept due to the noncomparative study design and unpublished sources. The ICER Draft Report noted this was grey literature and has cited an abstract recently presented at the 2016 American Academy of Dermatology meeting (Reich AAD 2016-cited in ICER references as #65). The report further makes comparative statements about this study in 8 different places in the "Comparative Clinical Effectiveness" section including almost 20% of the "Comparative Clinical Effectiveness Conclusion" language. This conclusion section has a long discussion about this study and the indirect evidence between apremilast and etanercept, and concludes that the products are "functionally equivalent for all other comparisons" within the Draft Report. There are a number of problems with this conclusion:

1. The purpose of this Phase 3b Safety and Efficacy Study of Apremilast to Treat Moderate to Severe Plaque Psoriasis is to test the clinical effectiveness and safety of apremilast compared with placebo as well as etanercept compared with placebo in the same group of patients with moderate-to-severe plaque PsO. (ClinicalTrials.gov NTC01690299). An etanercept comparison is not an objective of this study as it was meant to be an apremilast vs placebo comparison. In fact, none of the primary or secondary outcome measures listed in the clinicaltrials.gov file list a comparison between apremilast and etanercept, only comparisons of apremilast with placebo.

2. The grey literature abstract from AAD specifically states "This study was not powered for APR vs ETN comparisons." This statement in a published source should make ICER pause at the credibility of any statements in the report regarding comparative results.

3. The study lists, and ICER has noted, that the etanercept dose used in the LIBERATE study was not the labeled starting dose. Instead, the study used the etanercept 50 mg maintenance dose, which further makes this comparison biased. Additionally, while a 50 mg syringe dosage form is available, the study used 2 - 25mg syringes unduly increasing the patient burden and likely affecting the quality-of-life assessments.

4. In the conclusion of Section 4, ICER states "While the addition of the indirect evidence suggests an incremental benefit for etanercept, we feel that indirect findings can only confirm or downgrade certainty in evidence ratings." The difference between etanercept and apremilast in the indirect NMA for PASI 75 is significant as shown in Table G3. Dismissing this significant difference between these two drugs would invalidate this table for all drugs, and should make ICER conclude they are all equivalent, which clearly is <u>not</u> the case. This insignificant finding in the indirect NMA may be due to the appropriate etanercept dose being evaluated in the NMA studies compared to the LIBERATE study. The arbitrary nature of the decision to assume the indirect comparison is not valid negates the entire credibility of the indirect comparison and its use in the economic model.

Given these study design issues, the unpublished data, and improper interpretation of the indirect comparison, Amgen requests ICER remove this study from the Draft Report, including the following:

ICER Draft Report	Description
Page 26	"including a Phase IIIb trial [LIBERATE] comparing apremilast to a maintenance dose of etanercept that has not yet been published but was available in the grey literature."
Page 28	"LIBERATE" from Table 4
Page 29	"and there was no significant difference between etanercept and apremilast."
Page 30	"In one trial, there was no statistically significant difference between etanercept and apremilast (48% vs. 40%; p = 0.26)."
Page 31	Table 6 rows listing LIBERATE and Etanercept and Apremilast PASI 75 results
Page 34	" and LIBERATE. …., and apremilast
Page 35	Table 7 rows listing LIBERATE and Etanercept and Apremilast DLQI results "The LIBERATE trial comparing apremilast and etanercept was the only available head-to-head study. The proportion of patients achieving a minimum 5-point DLQI reduction for patients with at least a score of 5 on the DLQI at baseline was reported in one abstract, not statistically evaluated, and numerically the same as etanercept (23%)" "while apremilast was numerically similar to etanercept on the VAS-itch;"
Page 36	"In the LIBERATE trial, patients experienced a statistically significantly greater mean reduction on the VAS-itch scale from baseline for both apremilast (-35.6mm, p=0.00261) and etanercept (-36.4cm, p<0.0001) compared to placebo; the active intervention groups were not compared statistically, however, and the decrease was numerically higher for etanercept."
Page 47	"In the LIBERATE trial, patients experienced a statistically significantly greater mean reduction on the VAS-itch scale from baseline for both apremilast (-35.6mm, p=0.00261) and etanercept (-36.4cm, p<0.0001) compared to placebo; the active intervention groups were not compared statistically, however, and the decrease was numerically higher for etanercept."

Anthem

Submitted electronically via: publiccomments@icer-review.org

October 20, 2016

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Re: ICER Releases Draft Evidence Report on Treatments for Plaque Psoriasis

To Whom It May Concern:

Anthem is working to transform health care with trusted and caring solutions. Our health plan companies deliver quality products and services that give their members access to the care they need. With over 73 million people served by its affiliated companies, including nearly 40 million enrolled in its family of health plans. For more information about Anthem's family of companies, please visit www.antheminc.com/companies.

Overall, we believe the findings in this Draft Evidence Report are helpful and informative as part of a broader conversation on the value of these important therapies with introduction of new products to treat adults with moderate-to-severe plaque psoriasis. Additional insight from patients and advocacy groups provided in your review helps us in understanding current concerns of this population as it relates to UM managements strategies; such as, current step therapy strategies.

As it relates to the findings contained in this study, we would like to share a couple of comments to pass along.

1. We recommend caution in generalized statements that if read without the detailed information or if read by someone who that knowledge of the studies could be misinterpreted. Example: Page 33 of the printed document says in the summary statement-

    - **All immunomodulators showed statistically significantly higher proportions of patients with Physician Global Assessment (PGA) or Investigator's Global Assessment (IGA) of 'clear/almost clear' than**

placebo at the primary end point of each trial. Head-to-head trials found that etanercept and ustekinumab had lower PGA response rates than biologic comparators.

- **Anthem comment:** Stelara has some data showing lower response rates related to some of the new agents like Cosentyx or brodalumab, but no direct evidence showing it has lower response rates compared with Remicade or Humira. We recommend clarifying this statement. This could be interpreted that both Enbrel and Stelara are lesser options to all other biologics for this endpoint. However, what the studies showed and the report detailed out is that data showed Enbrel had lower response rates than Stelara, Cosentyx or Taltz in head-to-head trials. Similarly, Stelara had slightly lower response rates than Cosentyx or brodalumab in head-to-head trials.

2. In the print document on ***pages 218 and 219*** there is a stepwise table comparing effects of the various products. Erelzi the biosimilar to Enbrel is included and the table appears to indicate it is less efficacious compared to Enbrel. Given that the FDA has determined that it is approved as a biosimilar, which means there are no clinically meaningful differences relative to the reference product Enbrel, inclusion in the table in this way is slightly confusing and if read individually may lead someone to conclude it is less efficacious. Biosimilars to Humira and Remicade were also not included. We recommend you clarify this information.

***

We thank you for the opportunity to comment during this review process. Should you have any questions or wish to discuss our comments further, please contact Alan Rosenberg at (312) 234-7026 or Alan.Rosenberg@Anthem.com or Vicki Fisher at or (910) 725-1041 Vicki.Fisher@anthem.com .

Sincerely,

Vicki Fisher, PharmD, Director, Clinical Analytic Strategies
Clinical Pharmacy Policy, Anthem, Inc.
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October 20th 2016

RE: Comments to NE CEPAC document "Draft Evidence Report: Targeted Immunomodulators for the Treatment of Moderate-to-Severe Plaque Psoriasis Effectiveness and Value".

Dear Mr Dreitlein / Ms Segel,

Thank you for the opportunity to provide comments to the recently published draft evidence report "Targeted Immunomodulators for the Treatment of Moderate-to-Severe Plaque Psoriasis". The report confirms our position that apremilast is a cost-effective treatment option for patients suffering from moderate-to-severe plaque psoriasis.

We found a number of factual inaccuracies in this analysis, which would have a material impact on the incremental cost-effectiveness ratios that have been reported. Our detailed comments for your consideration are:

1. Page 30, Table 5 and repeated on Page 211, Table F1: citing Papp 2015, states that the placebo PASI 75 response is 15% in the apremilast trial. This is incorrect: the actual response rate reported in the Papp 2015 publication is 5.3% [1].

2. Page 17: States "NICE does not recommend apremilast, which it felt was poor value". NICE issued a draft positive recommendation for apremilast in July 2016 (This draft recommendation, Appraisal Consultation Document[2], was posted on the NICE website on July 2016). In fact the final appraisal determination, recommending the use of apremilast in patients with chronic plaque psoriasis, was posted on the NICE website earlier this week (NICE apremilast Final Appraisal Determination)[3].

3. Page 38, Table 8: States there was 0.1% treatment-related deaths in apremilast trials. To clarify; there was 1 death in the ESTEEM 1 trial, but there was no definitive relationship to study drug.

4. Page 53: States "we assumed that each infliximab administration used five 100 mg vials to account for incomplete vial usage (drug wastage)". However on page 53 (Table 14), the infliximab maintenance cost calculation indicates that only 4 vials have been considered, resulting in a cost of $2,143. The maintenance cost for 5 vials should be $2,679 per month.

5. Page 53, Table 14: Apremilast monthly cost is calculated assuming a 30.5 day month, while biologics monthly costs assume a 28 day month. The monthly cost calculation in the model is inconsistent and leads to incorrect incremental cost-effectiveness ratios. ICER should apply a standard definition of how many days constitute a month, and apply the daily price of the SKU of each product.

6. Page 53, Table 14: Infliximab price is quoted as $1,071.48 per vial. This price is outdated. The current infliximab price (as of Sept 29, 2016) is $1,113.27 per 100mg vial.

7. Page 53, Table 14: the ustekinumab calculation assumed that 30% of patients were greater than 100kg and therefore would receive a 90 mg dose (based on data from ustekinumab trials). Real-world U.S. data suggest that approximately 45% of patients received the 90mg ustekinumab dose [4]. A more robust cost analysis on ustekinumab should be applied to reflect the weight-based costs of ustekinumab in the real-world.

8. Page 214, Table F5 suggests patients receiving apremilast will have a renal test at initiation. Although there is a need for dose adjustment in patients with severe renal impairment, there is no requirement for renal screening or monitoring at treatment initiation in the apremilast label [5].

Other data inaccuracies specific to apremilast in the report include:

1) Page 29: References #72 (ESTEEM-1) and #61 (ESTEEM-2) should be used

2) Page 29: the absolute proportion of patients achieving PASI 75 above placebo within apremilast trials should be 23% - 28% (not 13% - 18%) [1,6]

3) Page 30: Table 5: PASI-90 Tx response should be 9-10 (not 9-94) and placebo should be 1-2 (not 0-2) [1,6]

4) Page 33: sPGA response range for apremilast should be 20% - 22% (not 20% - 47%) [1,6]

5) Page 35: clinically-meaningful improvements on the DLQI (defined as at least a 5-point reduction) is significantly different from placebo in both ESTEEM studies [1,6]

6) Page 35: DLQI MCID response was 65% for APR and ETN in LIBERATE (not 23%). [7]

7) Page 35: on itch VAS, APR was better than ETN at Week 2, but not at Week 16. [7]

8) Page 45: 2nd paragraph, “apremilast” should likely read “adalimumab”

Thank you for the opportunity to provide comments. Otezla is a valuable treatment option for many psoriasis patients who prefer a safe oral agent with a proven efficacy and tolerability profile. We would welcome the possibility to explain directly via a teleconference Otezla's unique value and our comments on this assessment.

Sincerely yours,

Frank Zhang
Global Pricing and Market Access
Inflammation & Immunology Franchise
Celgene Corporation

REFERENCES

1. Papp K, Reich K, Leonardi CL, et al. Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: Results of a phase III, randomized, controlled trial (Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM] 1). Journal of the American Academy of Dermatology. 2015;73(1):37-49.
2. https://www.nice.org.uk/guidance/GID-TA10084/documents/appraisal-consultation-document
3. https://www.nice.org.uk/guidance/GID-TA10084/documents/final-appraisal-determination-document
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6. Paul C, Cather J, Gooderham M, et al. Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate-to-severe plaque psoriasis over 52 weeks: A phase III, randomized controlled trial (ESTEEM 2). British Journal of Dermatology. 2015;173(6):1387-1399.
7. Green L, Thaci D, Zhang Z, Goncalves J, Nograles K, Nikkels A. Effect of apremilast and etanercept on pruritus and health-related quality of life in patients with moderate to severe plaque psoriasis: Results from the LIBERATE study. Journal of the American Academy of Dermatology. 2016;74(5):AB245.

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October 5, 2016

RE: ICER's draft evidence report, "Targeted Immunomodulators for the Treatment of Moderate-to-Severe Plaque Psoriasis: Effectiveness and Value."

Dear Dr. Pearson:

Founded in 1995 and based in Bowie, MD, the COSHAR Foundation Inc. works to improve the health outcomes of underserved communities through awareness-building, education, health programs and advocacy. Our mission is to address the pervasive health disparities affecting ethnic minorities, the elderly and the poor through greater access to prevention, testing and screenings, early diagnosis and optimal treatment. Accordingly, a large part of our work is centered on support and guidance to a network that we created, the National Health Ministry Network (NHMN), comprising over 40,000 plus houses of worship/churches and community-based organizations in the 50 states and Puerto Rico and the Virgin Islands that collectively reach millions of people with needed health information. We deliver our programs in a way that is culturally sensitive and health literate and thus, the organization has a track record of making a positive impact on the lives of those who need help the most.

When policymakers and the public health community consider the unequal burden of disease among underserved populations, the focus is usually on sickle cell anemia, viral diseases like AIDS and hepatitis C, and such common chronic diseases as heart disease, stroke, hypertension, and diabetes. However, we cannot ignore other conditions that have a significant health impact, physical manifestations, and by the mere nature of the symptoms, have stigma and shame attached. This includes psoriasis where the burden on minority populations, and especially the higher rates of misdiagnosis and non-treatment in African Americans and Hispanics are not well appreciated. It is for this reason that our organization offers these comments to the Institute for Clinical and Economic Review (ICER) regarding ICER's draft evidence report, *Targeted Immunomodulators for the Treatment of Moderate-Severe Plaque Psoriasis*.

ICER's draft report identifies Asians as a population of special interest but overlooks recent epidemiological data, such as the 2009-2010 National Health and Nutrition Examination Survey (NHANES), which shows that the populations most affected by psoriasis are Caucasians (3.6 percent), African Americans (1.9 percent), and Hispanics (1.6 percent),[i] with prevalence rates among blacks considerably higher than two decades ago. Further, studies demonstrate major differences in the extent and severity of psoriasis among racial and ethnic groups. For example, a large retrospective study found Caucasians have the lowest body surface area (BSA) involvement of psoriasis at 28 percent. In comparison, the mean BSA scores were 31.71 percent, 32.69 percent and 41.39 percent respectively in African Americans, Hispanics/Latinos, and Asian psoriasis patients.[ii]

Research also shows that racial groups, and especially African Americans, experience higher rates of severe psoriasis than whites,[iii] increasing the risk for cardiovascular disease, diabetes, hypertension, metabolic syndrome, stroke and other comorbid conditions in individuals who are already affected disproportionately by these life-threatening diseases. Further, studies document poorer quality of life measures among African American and Hispanic/Latino psoriasis patients. This includes a large survey of 4,725 people with psoriasis conducted by the National Psoriasis Foundation (NPF), which finds that 72 percent of minorities experience substantial quality-of-life challenges, including feelings of self-consciousness, embarrassment, anger, frustration, and helplessness[iv] that can lead to depression, alcoholism and substance abuse, and thoughts of suicide. These findings are of great importance to our foundation and the millions of lives that we serve. We cannot overlook these factors and do believe that this population is often misdiagnosed and certainly is underdiagnosed.

Additionally, because psoriasis can negatively impact most daily activities – such as using one's hands, sitting, walking and standing for long periods of time – the disease impedes mobility and worker productivity and leads to high rates of absence through psoriasis-related illness.[v] According to a recent report from the International Federation of Psoriasis Associations, Americans with psoriasis lose approximately 56 million hours of work a year. In communities of color where many of the workers are paid on an hourly basis, this has a tremendous impact on an already tenuous financial situation.

Taken together, these statistics underscore the need for timely diagnosis and effective treatment to improve the quality of life among psoriasis patients and to prevent the comorbidities that can lead to increased health expenditures and premature death. Unfortunately, as evidenced by a 2007 NPF survey of 1,142 adults with moderate or severe psoriasis, nearly 40 percent of these patients are not receiving any treatment and more than half are not being treated as recommended by American Academy of Dermatology guidelines,[vi] which encourage tailoring therapies to meet individual patient needs. Factors contributing to no or limited treatment include health insurance coverage restrictions and cost, fear of biologics, concerns about side effects, and lack of access to health care.

In light of these findings, the COSHAR Foundation and its partners urge ICER to consider the unmet needs of underserved patients already at higher risk for severe psoriasis and its comorbidities when considering the "value" of new disease-altering therapies that been demonstrated effective in improving patient outcomes. Especially because psoriasis is a hard-to-treat disease that can change form over time and has an unpredictable course of symptoms, the "value" of new therapies should reflect the savings to the health system from reducing the burden of psoriasis, which was estimated to cost the nation between $112 billion and $135 billion in 2013, according to a 2015 review published in *JAMA Dermatology*.[vii] This included indirect costs for lost productivity of between $23.9 billion to $35.4 billion and $36.4 billion to the health system for the medical comorbidities associated with psoriasis.

From the perspective of the minority health community, treating challenging autoimmune and inflammatory diseases like psoriasis requires greater access to new therapies that optimize patient care and reduce the impact of psoriatic disease.

Thank you for your consideration of this information.

Sincerely,

Sharon Allison-Ottey, MD

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[i] Rachakonda TD, Schupp CW, Armstrong AW. Psoriasis prevalence among adults in the United States. J Am Acad Dermatol. 2014; 70:512–516.

[ii] Shah SK, Arthur A, Yang YC, Stevens S, Alexis AF. A retrospective study to investigate racial and ethnic variations in the treatment of psoriasis with etanercept. J Drugs Dermatol. 2011; 10:866–872.

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[iv] Adegbidi H, Atadokpede F, do Ango-Padonou F, Yedomon H. Keloid acne of the neck: epidemiological studies over 10 years. Int J Dermatol. 2005;44(Suppl l):49–50

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October 12, 2016

Steven D. Pearson, MD, MSc, FRCP
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Re: ICER Review of Treatment Options for Plaque Psoriasis: Effectiveness, Value and Value-Based Benchmarks

Dear Dr. Pearson:

HealthyWomen (HW), a non-profit organization that serves as the nation's leading independent health information source for women, appreciates the opportunity to provide feedback in response to the Clinical and Economic Review's (ICER) draft evidence report entitled *Targeted Immunomodulators for the Treatment of Moderate-to-Severe Plaque Psoriasis: Effectiveness and Value.*

Affecting an estimated 7.5 million Americans,[1] psoriasis is a hard to treat chronic autoimmune disease with an unpredictable course of symptoms, often resulting in incorrect or delayed diagnoses and insufficient access to care. When this happens and the disease is not kept in check, patients face periods of extensive flaking and bleeding of their skin, accompanied by intense pain, extreme itching and fatigue.

Research further demonstrates that if the disease goes untreated or undertreated, up to 30% of psoriasis suffers may develop psoriatic arthritis, an inflammatory form of arthritis that can lead to irreversible joint damage.[2] Yet, data show that a large number of psoriasis suffers are not receiving treatment. As reported in a 2013 study, 23.6% to 35.5% of patients with moderate psoriasis and 9.4% to 29.7% of patients with severe psoriasis did not receive treatment during the years 2003 to 2011. Further, the study found that among patients receiving treatment, 29.5% with moderate psoriasis and 21.5% with severe psoriasis were only given topical agents.[3]

Of added concern, research correlates psoriasis with the increased risk of other inflammatory diseases, such as arthritis, heart disease/hypertension, diabetes, Crohn's Disease, lupus, irritable bowel syndrome, depression, and obesity.[4] This is especially the case for the estimated 10% of psoriasis suffers with severe

[1] Menter A, Gottlieb A, Feldman SR, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. J Am Acad Dermatol 2008 May;58(5):826-50
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[3] Armstrong AW1, Robertson AD, Wu J, Schupp C, Lebwohl MG. Undertreatment, treatment trends, and treatment dissatisfaction among patients with psoriasis and psoriatic arthritis in the United States: findings from the National Psoriasis Foundation surveys, 2003-2011. JAMA Dermatol. 2013 Oct; 149(10):1180-5.
[4] National Psoriasis Foundation.

disease,[5] where new biological-based drugs can play an important role in reducing these risks and the toll of psoriasis on the nation's health system. As reported in a January 2015 *JAMA Dermatology* article, psoriatic disease costs the nation up to $135 billion a year in medical expenditures, lost productivity and to treat psoriasis-related comorbidities.[6]

The good news for patients and clinicians is that research has resulted in a number of innovative, more effective therapies that have greatly improved the treatment of psoriasis. Thus, today, health providers can choose among topical drugs, phototherapy, traditional systemic medications, biologics that work by blocking some functions of the immune system and novel oral therapies that correct the overactive immune response that causes inflammation in people with psoriasis and psoriatic arthritis. Having access to all these options is necessary because people respond differently to specific regimens and effective therapies can stop working due to treatment resistance.

With this goal in mind, HealthyWomen urges ICER to keep patients in mind when finalizing its evidence report on psoriasis therapies. Timely, effective diagnosis and treatment of psoriasis are medical and economic necessities. Thus, it is essential that the needs of patients not be undervalued.

Thank you for taking these comments into consideration.

Sincerely,

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[5] Pariser, DM, Bagel, J, Gelfand, JM, Kormann NJ, et al. "National Psoriasis Foundation Clinical Consensus on Disease Severity". ARCH DERMATOL. Vol. 143, Feb. 2007.

[6] Sivamani RK, Correa G, Ono Y, Bowen MP, Raychaudhuri SP, Maverakis E. Biological therapy of psoriasis. *Indian J Dermatol*. 2010;55(2):161-170

October 20, 2016

Submitted electronically to: publiccomments@icer-review.org

Steven D. Pearson, MD, MSc
President
Institute for Clinical and Economic Review
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Re: Feedback on ICER's Psoriasis Draft Evidence Report

Dear Dr. Pearson:

On behalf of the Institute for Patient Access, I thank you for the opportunity to provide feedback on the Institute for Clinical and Economic Review's draft report on the comparative clinical effectiveness and value of targeted immunomodulators for adults with moderate-to-severe plaque psoriasis.

About the Institute for Patient Access

The Institute for Patient Access (IfPA) is a physician-led policy research organization dedicated to maintaining the primacy of the physician-patient relationship in the provision of quality healthcare. To further that mission, IfPA produces educational materials and programming designed to promote informed discussion about patient access to approved therapies and appropriate clinical care. IfPA was established in 2012 by the leadership of the Alliance for Patient Access, a national network of nearly 700 physician advocates committed to patient access. IfPA is a 501(c)(3) public charity non-profit organization.

Feedback on Draft Report

As ICER's draft report acknowledges, plaque psoriasis is a common disease that can impact patients' quality of life and daily functioning. With no cure available, patients have historically managed the condition with therapies such as methotrexate. Newer targeted and biologic therapies, however, can improve the duration and level of symptom relief that patients can achieve.

In the interest of patients' ability to access these treatments, IfPA is pleased that ICER's analyses show all targeted agents to be cost-effective and to carry a budget impact below ICER's limit.

IfPA does have concerns, however, that ICER's conclusions diverge from the results of its analyses. Specifically, IfPA finds it problematic that ICER concludes:

1. *"Targeted agents other than infliximab do not represent good economic value unless drug rebates and work productivity impacts are assessed, in which case they are moderately cost effective*." ("Summary and Comments," page 66)

   When compared to initial non-targeted therapy, the cost-effectiveness ratios of all agents fall under (or very close, in the case of etanercept) the threshold used by ICER. Therefore, it is unclear why ICER concludes that only infliximab represents "good economic value."

   In this analysis of targeted therapy for psoriasis, cost-effectiveness ratios do not provide a basis for discriminating among treatments.

2. "*…differentiating which targeted agent should be used first-line is highly dependent on the rate of second-line targeted drug use"* and *"If second-line targeted drug use is high, our findings suggest the main means of discriminations among agents should be price*." ("Summary and Comments," page 66)

   No credible results are presented to support these findings. Moreover, it is difficult to understand how the possible results of unknown future decisions (such as the choice of second-line therapy) should affect current decisions (in this case, the first-line choice). It is even more perplexing that the impact would be to change the criterion for the first decision.

In addition, IfPA observes from this draft report that safety profiles and routes of administration for the treatments, aspects that can significantly impact patients' quality of life, were not incorporated in the model. As described on page 56, "Utilities," the safety profiles of the treatments were not incorporated in the model because of "similar adverse event profiles between drugs and the absence of their utility evaluation in other cost-effectiveness analyses in psoriasis." Mode of administration was not modeled.

ICER consulted patient advocacy groups, and they voiced challenges with current therapies – specifically poor tolerability and inconvenience – particularly with applying topical agents and with multiple injections. These are important aspects that should have been incorporated in the model, as they do affect patients' quality of life. ICER cites the PSOLAR observational study comparing the rates of infections among patients treated with targeted therapies. The findings of this study were "notable differences among treatments," which contradicts ICER's statement of "similar adverse event profiles."

The impact of the differences in the route of administration, an aspect judged to be relevant by the patients and an important differentiator among the treatments should have

been analyzed as well. Missing aspects such as route of administration and safety may have substantial influence on the results and are inadequately considered in this draft.

Conclusions

I urge you to consider the input provided here as ICER prepares a final report. If we may provide further detail or aid the Institute for Clinical and Economic Review in incorporating any of the above recommendations, please contact us at 202-499-4114.

Sincerely,

Brian Kennedy
Executive Director

October 18, 2016

Institute for Clinical and Economic Review
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RE: Open comment on Draft Evidence Report on Treatments for Plaque Psoriasis
Sent via: publiccomments@icer-review.org

On behalf of the International Psoriasis Council (IPC), we welcome the opportunity to comment on the draft ICER report. As an international society representing 100 key opinion leaders from 28 countries, and committed to improving access to dermatologic therapies around the world, we feel it is important to call attention to a few points raised by the analysis.

Methodologically, one of the issues over time is loss of response or need for dose escalation. Since patients with psoriasis are likely to be on the medication for years the most relevant cost analysis is a long-term evaluation. While data for those endpoints are less robust because they cannot typically be generated in controlled clinical trials, data from registries suggest that this analysis would likely alter some of the recommended choices in this report. For example, the efficacy of infliximab at 5 mg per kg declines from 80% to 50% by the end of the first year and therefore often requires substantial dose escalation.

But most importantly, it is critical to recognize that the medications discussed in this report profoundly improve the lives of our patients. It was only 15 years ago that the state of the art for treatment of psoriasis included covering people in tar based products for 40 hours every week and hospitalization. Treating psoriasis today is a completely different experience.

This is not a case of an expensive therapy providing marginal benefit; these medications take patients, who are literally covered with skin disease from head to toe, and relieve them almost entirely of that burden for long periods of time. Since modest decreases in the costs of the therapies or changes in the methodology appear to substantially affect the analysis of the economic valuation we caution urgently against using evaluations like these to further restrict access to these extraordinarily effective medications.

We appreciate your consideration of our comments and are open to further discussions.

Sincerely,

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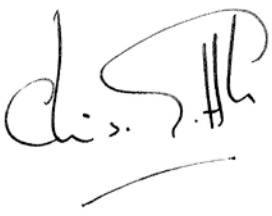

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ICER DRAFT REPORT -- PUBLIC COMMENTS

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BACKGROUND

- **Page 4; Figure 2:** an anti-IL-23 agent (only one in its class)
- **Page 4:** Immunomodulatory should be immunomodulator

TOPIC IN CONTEXT

- **Page 9; Table 1: DOSING for REMICADE:** The recommended dose of REMICADE is 5 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter for the treatment of chronic severe (i.e., extensive and/or disabling) plaque psoriasis. (REMICADE Prescribing Information)
- **Page 10; 2nd paragraph:** Live vaccines or therapeutic infectious agents – should not be given with REMICADE. Bring pediatric patients up to date with all vaccinations prior to initiating REMICADE. At least a six month waiting period following birth is recommended before the administration of live vaccines to infants exposed in utero to infliximab (REMICADE Prescribing Information)
- **Page 10; Table 1: DOSING for TALTZ:** 160mg subcutaneously at week 0, then 80mg at weeks 2, 4, 6, 8, 10, 12 then 80mg Q 4 weeks. Please ensure that all models include correct dosing for all products.
- **Page 10; 3rd paragraph:** For the anti-IL-17A agents, concerns have included infections and reactivation of latent TB, **inflammatory bowel disease, and hypersensitivity reactions** for secukinumab; **infections, reactivation of TB hypersensitivity reactions**, neutropenia, candidal infection, and inflammatory bowel disease for ixekizumab. Limited modelling of these known adverse events could bias economic results.
- **Page 10; 4th paragraph:** Report includes lymphoma association with ustekinumab, however, an evaluation of safety and efficacy in three (1 phase 2 and 2 phase 3) randomized, double-blind, placebo-controlled trials of STELARA in 3117 plaque psoriasis patients through year 5 determined that lymphoma (SIR = 0.80; 95% CI 0.10–2.91) occurred in two patients: one pre-existing cutaneous T-cell lymphoma at study entry misdiagnosed as psoriasis, and one possible case of Hodgkin disease based on autopsy findings in a patient who died from traumatic bowel perforation, as previously reported. (Papp et al, 2013)

SUMMARY OF COVERAGE POLICIES & CLINICAL GUIDELINES

- **Page 16; Clinical Guidelines:** The most recent guidelines from the American Academy of Dermatology (AAD) were published in 2011 entitled "Guidelines of care for the management of psoriasis and psoriatic arthritis" (J Am Acad Dermatol 2011;65:137-74) and support the use of STELARA in healthy adult males and women of childbearing potential using contraception after topical therapy when UV not available in healthy males and UVB not available in women of childbearing potential using contraception. (Menter et al, 2011)
- **Page 17; NICE Guidelines:** Please revise the summary of NICE guidelines to accurately describe their recommendation for ustekinumab. https://www.nice.org.uk/guidance/ta180/chapter/1-Guidance
- **Page 19, Table 2**: The summary reflects regional recommendations for New England which cannot be generalized and applied to other regions across the nation

COMPARATIVE CLINICAL EFFECTIVENESS

- **Page 22; Table 3: DOSING for REMICADE:** The recommended dose of REMICADE is 5 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter for the treatment of chronic severe (i.e., extensive and/or disabling) plaque psoriasis. (REMICADE Prescribing Information). Please make sure all models are accurate with regard to product dosing.
- **Page 24; Please correct:** We also looked for studies evaluating biosimilar forms of the anti-TNF agents. No peer-reviewed data are available, but a brief description **ofof** an etanercept and adalimumab biosimilars **areareare biosimilar** are described in the Emerging Therapies section of this report.

ICER DRAFT REPORT -- PUBLIC COMMENTS

- **Page 28; Table 4:** Infliximab total patients should be 1213; PASI (mean) should be 21; Previous biologics (%) should be 15
- **Page 28; Table 4:** Ustekinumab PASI (mean) should be **20**
- **Page 29, 1st paragraph (2nd to last sentence):** Lebwohl et al (2010) evaluated pooled data from PHOENIX 1 (n=766) and PHOENIX 2 (n=1230) to examine the impact of weight on STELARA efficacy, safety, and pharmacokinetics (Lebwohl et al, 2010)
- **Page 30; Table 5:** Ustekinumab PASI 90 score from PHOENIX 1 (Leonardi et al, 2008) for STELARA 45mg = 41.6% (106/255) and PASI 90 score from PHOENIX 2 (Papp et al , 2008) for STELARA 45mg = 42.3% (173/409)
- **Page 30; Table 5:** Ustekinumab PASI 100 score from PHOENIX 1 (Leonardi et al, 2008) for STELARA 45mg = 12.5% (32/255) and PASI 100 score from PHOENIX 2 (Papp et al , 2008) for STELARA 45mg = 18.1% (74/409)
- **Page 31; Table 6. Comparative Trials: PASI Responses –** Ustekinumab WBD but efficacy is not reported by weight based.
- **Page 32; 3rd paragraph**: secukinumab spelled incorrectly
- **Page 35**; Other quality of life measures. Missing Ustekinumab SF-36 data and PRO data
- **Page 37**; 3rd paragraph: WLQ domains for output demands (6.8/7.0 vs. **-1.1**)
- **Page 38;** 1st paragraph: Should read: "In addition, a publication which pooled patients from PHOENIX 1 and 2 reported that, at week 12, the proportion of patients with impaired sexual function was statistically significantly higher with placebo (23.0%) (which remained unchanged from baseline) compared with ustekinumab 45/90mg (2.6/2.8%) ($p<0.001$). A similar pattern of improved sexual function was observed at weeks 24 and 28 among patients in the placebo group who crossed over to treatment with ustekinumab at week 12." (Guenther et al)
- **Page 39; Table 8:** Rates of adverse events listed during placebo controlled period for ustekinumab do not appear to be consistent with rates described in Section 6.1 of the Prescribing Information for STELARA (STELARA Prescribing Information)
- **Page 40; 3rd paragraph:** The cumulative safety experience of STELARA was analyzed in patients with up to 5 years of treatment across phase 2 (n=301/320) and phase 3 (PHOENIX 1 [n=753/766], PHOENIX 2 [n=1212/1230], and ACCEPT [n=851/903]) PsO clinical trials.
  SAEs were observed at a rate of 7.0, 7.2, and 7.1 in the STELARA 45-mg, 90-mg, and combined groups, respectively. Number of events of serious infection per 100 PY with 95% CIs were 0.98 (0.69-1.35), 1.19 (0.91-1.52), and 1.10 (0.89-1.34) for 45-mg, 90-mg, and combined groups, respectively. Cumulative rates of NMSC per 100 PY with 95% CIs were 0.64 (0.41-0.95) for 45-mg, 0.44 (0.28-0.66) for 90-mg, and 0.52 (0.39-0.70) for the combined group. Additionally, the rates of malignancies other than NMSC per 100 PY were 0.59 (0.37-0.89) for 45-mg, 0.61 (0.42-0.87) for 90-mg, and 0.60 (0.45-0.78) for the combined group. The rates of other malignancies were consistent with the expected incidence in the general US population, using the SEER database adjusted for age, gender, and race. The number of events of MACE per 100 PY with 95% CIs were 0.56 (0.35-0.85) for the 45-mg, 0.36 (0.22-0.57) for the 90-mg, and 0.44 (0.32-0.61) for the combined groups. (Papp et al, 2013)
  Page 40; 4th paragraph: As of August 23, 2014, 12,093 patients (40,388 patient-years) were enrolled in PSOLAR. Unadjusted rates of malignancy were: STELARA 0.48 events per 100 PY (60 events/12472 PY); anti-TNF sponsor biologics (REMICADE/SIMPONI) 0.79 per 100 PY (41/5176 PY); nonsponsor biologics (almost exclusively etanercept and adalimumab) 0.73 per 100 PY (116/15991 PY); and nonbiologic therapy 0.84 per 100 PY (57/6749 PY). Overall, 274 malignancies (0.68 per 100 PY [274/40388 PY]) excluding NMSC were reported across all treatment groups since registry inception. Unadjusted rates of serious infections per 100 PY for PSOLAR patients with exposure to therapy within the previous 91 days were as follows: STELARA-exposed patients = 0.93 (74/7944 PY); sponsor biologics (REMICADE) = 2.91 (96/3301); nonstudy sponsor biologics rates of serious infections = 1.91 (245/12833 PY); the rate of serious infections in patients with no biologic exposure = 1.43 (233/16322 PY). The unadjusted rate of serious infections in all patients was 1.60 (648/40389 PY). Unadjusted rates of MACE

per 100 PY for PSOLAR patients with any exposure to therapy were as follows: STELARA-exposed patients = 0.32 (40/12472 PY); sponsor biologics (REMICADE) = 0.33 (17/5176); nonstudy sponsor biologics rates of MACE = 0.28 (45/15991 PY); the rate of MACE in patients with no biologic exposure = 0.47 (32/6749 PY). The unadjusted rate of MACE in all patients was 0.33 (134/40388 PY). (Papp et al, 2015)

OTHER BENEFITS & DISADVANTAGES

- **Page 49:** With regards to other benefits and disadvantages, ICER has chosen to focus only on the method of administration and rapidity of response for the treatment of patients with PsO. However, it should also be noted that patient preference also includes other benefits such as durability of response, frequency of dosing, etc. (Gutknecht et al, 2016)

COMPARATIVE VALUE

- **Page 52:** ICER assumes that the probability of discontinuing newer drugs (secukinumab, ixekinumab, and brodalumab) is the same as ustekinumab. It should be noted that the discontinuation rates for ustekinumab are based on observed real-world estimates while there is currently limited data on discontinuation rates for the IL17A class of agents. ICER indicates that this assumption will be tested in sensitivity analyses, however among this class of agents, only a univariate sensitivity for ixekizumab is presented. This increases the uncertainty around the impact of this assumption for other IL17 agents. Additionally, the range of values tested for discontinuation in the univariate sensitivity analysis for ixekizumab is 12% to 20% (Table F7). It is unclear how the determination for this range was determined and justified.for ixekizumab. Additionally, there does not appear to be any discussion of the assumptions regarding the assumed discontinuation rates for the oral therapy apremilast.
- The rationales for the choices made with regards to modelling of adverse events are unclear. ICER states that "the costs for adverse events were not included in the base case analysis but were explored in sensitivity analysis" (Page 52). Additionally, ICER later states that they "…did not include any adverse events associated with disutilities", as well as noting "the cost of one serious adverse event, pneumonia, was included in scenario analyses to assess its relative importance" (Page 56). First, it is unclear as to the choice to model only SAEs for pneumonia which contrasts with a previous ICER statement that the adverse event profiles were "similar…between drugs" (Page 56 and Table 8, Page 39). Second, it appears that only the rates for upper respiratory infections (URIs) have been varied in the univariate sensitivity analyses of infliximab and ixekizumab (Figures 7 and 8) and not the other drugs, or any other adverse events. Finally, non-inclusion of disutilities and costs associated with AEs and SAEs could potentially systematically bias results towards interventions with worse AE profiles.
- **Page 66:** The ICER analysis draws three major conclusions, some of which may not be fully supported by the presented evidence. The conclusions of the ICER report are: first, infliximab is the most cost-effective intervention for psoriasis treatment; second, targeted agents, besides infliximab, are not "good economic value" unless drug rebates and improvements in work productivity are considered; and third that differentiating which targeted therapy should be used in first line is highly dependent on the rate of second line targeted use and that if second-line targeted use is high that the main means of discriminating is through price.
- With regard to the second conclusion, the ICER framework outlines three criteria for determination of probable high, intermediate, or low value, namely the estimated ICER, significant benefits or contextual factors, and potential budget impact. The estimated ICERs (Table 16) range from $110,431 - $157,723 per QALY and from $87,242 - $122,447 (Table 17) with a 20% discount on price from WAC. The impact of work productivity was only tested in one-way sensitivity analyses for ixekizumab and infliximab, and in both these models showed very modest impact on the estimated ICERs. With regards to significant benefits or contextual factors, biologic therapies have provided significant benefits to patients suffering from moderate to severe psoriasis, however there was very limited discussion in the ICER report on this key, as defined by ICER, criteria. Finally, with regards to budget impact, the report limited the analysis to brodalumab and ixekizumab and found that both of these interventions were well below (42 and 44%)

ICERs defined budget impact threshold. Based on the totality of evidence, the second conclusion does not appear to be supported based on the evidence presented by ICER.

- With regard to the third conclusion, all modelling exercises presented did not explicitly model the impact of true targeted second-line therapy and instead utilized averages for all second line biologic therapy. Additionally, it was assumed that 50% of first-line failure patients progress to non-targeted therapy in second-line and in the one-way sensitivity analyses for infliximab the conclusions were most sensitive to cost of non-targeted therapy, for infliximab, and highly sensitive to the cost of non-targeted therapy for ixekizumab. Limited sensitivity analysis and the exclusion of probabilistic sensitivity analysis make it difficult to draw conclusions based on the likely high degree of uncertainty around the presented point estimates.

APPENDICES

Leonardi et al

- **Page 159:** PASI 75(%): 1) 67.1, 2) 66.4, 3) 3.1
- **Page 159: PSO Duration**: 1)19.7, 2) 19.6, 3) 20.4
- **Page 160; PGA Cleared or minimal**: 1) 60.4, 2) 61.7, 3) 3.9% (all analyses P<0.0001 vs placebo)
- **Page 160: PsA**: 1) 29.0, 2) 36.7, 3) 35.3
- **Page 160: PGA Cleared or minimal**: 1) 60.4, 2) 61.7, 3) 3.9%
- **Page 160:** No deaths were reported through Week 76.

Kimball et al

- **Page 161:** PASI 10 (%) should be PASI 100 (%)

Papp et al

- **Page 161:** Overall N = 1230; UST 45 mg n= 409; UST 90 mg n= 411; placebo n = 410
- **Page 162: PASI 90 (%):** 1) 42.3, 2) 50.9, 3) 0.7
- **Page 162; Baseline PASI:** 1) 19.4; 2) 20.1; 3) 19.4

Langley et al

- **Page 163; Weight:** Information reported here is adjusters vs. non-adjusters; UST 45 mg and UST 90 mg treatment arms are not included in this table
- **Page 163; AEs at wk 264:** 1) 222, 2) 195, 3) 206
- **Page 163; SAEs (%):** a) 6.57, b) 7.43, c) 7.02

Reich et al

- **Page 167; WLQ-time management:** UST45= 8.0; UST90=10.2

Igarashi et al

- **Page 171; AEs ≥1 (%):**1) 65.6, 2) 59.7, 3) 65.6

Tsai et al

- **Page 172;** PHASE II/III should be PHASE III
- **Page 172; PsO duration (years):** 1) 11.9, 13.9

Zhu et al

- **Page 175; PsA (%):** UST 45 mg = 8.8%; Placebo = 8.6%

Papp et al (2015)

- **Page 184;** June 20, 2007 through August 23, 2014
- **Page 184;** Overall N= 12093; UST n = 4364; INF n = 1394; other biologics n = 4251; non-biologics = 2084; Patient-years = 40388
- **Page 184; % male**: 1) 47.2; 2)49.3; 3)48.8; 4)51.3
- **Page 184; PsA(%)** PsA (self-reported) 1) 34.1; 2)55.7; 3)39.5; 4)17.9; PsA (confirmed by joint specialist) 1) 15.2; 2)25.5; 3)13.5; 4)5.9
- **Page 184; Previous Biologic use:** 1) 87.9
- **Page 184; All-cause mortality:** 1) 0.41; 2)0.41; 3)0.42; 4)0.68
- **Page 184; MACE:** 1) 0.32; 2)0.33; 3)0.28; 4)0.47
- **Page 184; Serious Infection:** 1) 0.93; 2)2.91; 3)1.91; 4)1.43

Strober et al

- **Page 185; Age (years):** 1) 46.3; 2) 46.8; 3) 46.7; 4) 47.9
- **Page 185; Male (%):** 1) 56.8; 2) 56.0; 3)58.0; 4)62.9
- **Page 185; PsO Duration (years):** 1) 19.1; 2) 14.7; 3) 16.1; 4) 17.2
- **Page 185; PsA (%):** 1) 33.5; 2)35.8; 3) 35.0; 4) 44.0
- **Page 204-208: Ongoing studies:** No mention of ustekinumab for the PSOLAR study.
- **Page 216- Section G. Table G1-G9.** Erelzi (biosimilar of etanercept) is included in the table. It is out of the scope to include a biosimilar.

VOTING QUESTIONS

Please assure that all questions are posed in a consistent way and please be explicit around the comparisons between two interventions. All questions should ask first, whether sufficient evidence was provided in the report to make a decision regarding the discussion point, and then secondly ask if the evidence is sufficient to support the recommended ICER rating (questions 1 -6) or valuation (question 7).

QUESTION 1:

Comments: Question 1 misleadingly implies that infliximab and adalimumab are equivalent comparators vs. etanercept. All pairwise comparisons of net health benefit of infliximab to all other molecules (Table 12, Row 5) are strictly greater than the same comparisons for adalimumab (Table 12, Row 1). We would suggest revising the question to make all individual pair-wise comparisons (infliximab vs. adalimumab, infliximab vs. etanercept, adalimumab vs. etanercept, etc.) which is consistent with the evidence provided in Table 12, pg. 48.

QUESTION 3 & QUESTION 4:

Comments: Suggest combining questions 3 and 4 and changing wording to be consistent to prior questions to: "For patients with moderate-to-severe plaque psoriasis for whom topical therapies, older systemic therapies, or phototherapy have been ineffective, contraindicated, or not tolerated, is the evidence adequate to distinguish among the net health benefits of brodalumab vs. ustekinumab, ixekizumab vs. ustekinumab, secukinumab vs. ustekinumab, brodalumab vs. ixekizumab, brodalumab vs. secukinumab, ixekizumab vs. secukinumab." Additionally, a subsequent question, similar to question 1a, should be provided to determine, conditional on there being "adequate evidence to distinguish among the net health benefits," as to whether that evidence is sufficient to support the recommended rating proposed by ICER.

QUESTION 5 & QUESTION 6:

Comments: For questions 5 and 6, please define population and provide individual comparisons rather than grouping all targeted immunomodulators together and make consistent with prior questions.

QUESTION 7

Comments: Please define "long-term value," including time frame (e.g. 5-year vs. 10-year) and explanation of what constitutes value. Neither of the economic models in the report provides sufficient evidence to answer this question. For example, only one-way sensitivity analyses were provided for infliximab versus non-targeted therapy and ixekizumab versus non-targeted therapy. Therefore, there is no current way for a reviewer to determine the "long-term value" of these interventions, compared to non-targeted therapy, due to the high level of uncertainty. Additionally, the budget impact model was tested for ixekizumab and infliximab only. Additionally, this question should be consistent with the prior questions, namely: First has adequate information been provided to determine if there are meaningful differences in net health and cost benefits between all of these interventions, and, if yes, is that information sufficient to support the ICER recommendation.

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NHMA
National Hispanic Medical Association

October 18, 2016

Steven D. Pearson, MD, MSc, FRCP
President
Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston, MA 02109 USA

RE: ICER Assessment of Treatment Options for Plaque Psoriasis: Effectiveness, Value and Value-Based Benchmarks

Dear Dr. Pearson:

Established in 1994 and based in Washington, DC, the National Hispanic Medical Association (NHMA) represents the interests of 50,000 licensed Hispanic physicians who are on the front lines in addressing the health needs of almost 57 million Hispanics living in the U.S. as well as other underserved populations. Our goal is to serve as a resource for policymakers, health care providers and institutions such as the Institute for Clinical and Economic Review (ICER) on ways to strengthen health service delivery to Hispanic communities and to reduce the burden of diseases experienced by people of Hispanic or Latino origin, including such diverse subgroups
as Puerto Rican, Mexican, Cuban, Central and South Americans.

Although usually not considered a minority health issue, psoriasis represents a significant challenge for the Hispanic community and the physicians that take care of them. Accordingly, NHMA welcomes the opportunity to comment on ICER's draft evidence report on psoriasis treatments, especially to reflect the unmet needs of the estimated 1.6 percent of the Hispanic population[1] who now live with this serious autoimmune disease.

Because the medical literature contains few studies documenting psoriasis' negative impact on people of color, the disease is not well described in nonwhite populations. Yet, what is known to date is disturbing. It is well documented that psoriasis is significantly undertreated in the general population.

However, because psoriasis in darker skin types presents diagnostic challenges, the implications are greater for Latinos and other racial and ethnic minorities[1] who are more likely to go undiagnosed or misdiagnosed and receive suboptimal care. In addition, psoriasis differs in disease distribution and severity in Hispanics and African Americans compared to whites.

This finding was confirmed by a 2009 study by the National Psoriasis Foundation (NPF), which found that 10% to 23% of racial groups had very severe disease compared to 8% of whites.[1]

At the same time, because severe psoriatic disease is directly associated with a number of related comorbid conditions, Latino patients are at greater risk for serious diseases that already affect them at higher rates, such as diabetes, hypertension and obesity. According to data from the Centers for Disease Control and Prevention CDC), Hispanics are 50% more likely to die from diabetes, have 24% more poorly controlled high blood pressure, and have 23% more obesity than whites[1] – all diseases where psoriasis has a direct connection.

Hispanics and other nonwhite racial-ethnic psoriasis sufferers are also more likely to experience a poorer quality of life due to their disease, which can take the form of depression, anxiety, self-consciousness, impaired social functioning, reduced work productivity, higher BMI, smoking and alcohol use.[1] One disturbing result is a negative impact on employment. According to a 2013 European study, 42% of people with psoriasis faced reduced job prospects and 35% were passed are over for salary increases and job promotions.[1]

It is also well documented that psoriasis is a challenging disease where relapses and treatment resistance are common and medications that are effective for a time suddenly stop working. These problems are especially acute when the disease is severe and widespread or on areas like hands, feet or the scalp. As a result, trial and error are commonplace to determine the therapy that is most appropriate for each individual patient.

What these findings make clear is that effective diagnoses and treatment of psoriasis are necessary to reduce the toll of this disease on people's lives. Therefore, as ICER moves forward with its assessment of newly approved treatments for psoriasis, NHMA encourages the organization to consider the terrible burden on patients with severe disease and the many challenges for clinicians and patients when determining the most effective treatment. This means policies that increase, not restrict, access to the range of effective treatments that are available today, including all recently approved biologics and novel oral therapies that targeted specific aspects of the immune system.

Thank you for your kind consideration.

Sincerely,

Elena Rios, MD, MSPH
President and CEO
National Hispanic Medical Association

Our Mission: To drive efforts to cure psoriatic disease and improve the lives of those affected.

October 20, 2016

Steven D. Pearson, MD, MSc, President
Institute for Clinical and Economic Review
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Submitted via email: publiccomments@icer-review.org

RE: Public Comment on Draft Evidence Report *Targeted Immunomodulators for the Treatment of Moderate-to-Severe Plaque Psoriasis: Effectiveness and Value*

Dear Dr. Pearson,

On behalf of the more than 8 million Americans living with psoriatic disease, the National Psoriasis Foundation offers the following public comment on the Institute for Clinical and Economic Review (ICER) *Targeted Immunomodulators for the Treatment of Moderate-to-Severe Plaque Psoriasis: Effectiveness and Value Draft Evidence Report* released on September 29, 2016. Our comments build upon items raised over numerous calls and contained in NPF documents to ICER dated June 17th, July 8th, August 1st, and September 12th. Due to space constraints we do not revisit items addressed in those communications. As you move toward completing this assessment, we express our continued appreciation for ICER's willingness to engage the NPF in the process, and we hope the comments and concerns we raise are favorably addressed in the final report. While we appreciate that this assessment has included patients and providers, findings based on omissions and assumptions will only serve to grow the already unacceptable 55% of patients with moderate to severe psoriasis who are not being treated to the appropriate standards of care.[1]

The NPF was pleased that the draft report captured some of the significant, debilitating and frustrating challenges of living with and managing psoriatic disease. However, we remain concerned by a number of gaping omissions, assumptions, and value conclusions that we believe challenge the report findings. This response will touch on these concerns as follows. First, we will address concerns regarding the way ICER has discussed psoriasis, patient preferences and patient treatment concerns. Second, we will explore omissions and assumptions regarding treatment selection and administration. Third, we will explore the data used and assumptions made in the model and the impact on the conclusions ICER reached. Finally, we will address ICER's three main conclusions:

> (1) "Infliximab appears to be the most cost-effective targeted agent for psoriasis treatment, despite the necessity for intravenous administration" and that the conclusion is "robust to the several analyses that explored the uncertainty in the model";
>
> (2) "Targeted agents other than infliximab do not represent good economic value unless drug rebates and work productivity impacts are assessed" – where "value" is drug treatment cost per QALY and not relative to infliximab or other treatments; and

(3) "Differentiating which targeted agent should be used first-line is highly dependent on the rate of second-line targeted drug use."

Characterizing psoriasis and patient perspectives without accounting for the heterogeneity of psoriasis

Although psoriasis is such a prevalent immune-mediated disease, the serious and systemic nature of the disease is often misunderstood and goes unappreciated by those not personally impacted. In the introduction of the report, ICER fails to note the immune-mediated and systemic nature of psoriasis (except by reference to "other autoimmune diseases") and minimizes the serious nature of related comorbid health conditions. By limiting the description in this way – failing to include the immune-mediated origin of the disease – and focusing solely on the skin involvement in the opening sentence of the report and beyond, the report reinforces this misconception. While the background does note that "plaque psoriasis significantly decreases health-related quality of life," this discussion fails to include information about the impact of disease management on related health conditions or comorbidities as well as quality of life. The report also ignores data showing early mortality in patients with psoriasis remains elevated compared to the general population.[2]

Additionally, while the background section of the report notes that the location of psoriasis on the body can impact daily and/or social functioning and thereby decrease quality of life, the remainder of the report does not account for site considerations. The location of disease (face, genitals, soles/palms) is only given passing reference in discussions of topicals and patient preferences. The report generally lacks an acknowledgement of the heterogeneity of psoriatic disease – different locations, different systemic symptoms, different severity, and different response to different treatments – along with differing patient preferences. An NPF survey of more than 400 patients done in 2012 found that two-thirds of these respondents felt angry, frustrated, and/or helpless, and recent studies have demonstrated a significant association between psoriasis and depression, anxiety, and suicidal ideation.[3] The brief discussion of the psychological and emotional effects of the disease in the overview is limited and fails to address significant impact of psoriatic disease on mental health.

We commend ICER for including in the report insights gained from patients and the National Psoriasis Foundation. As we have shared through numerous calls, emails and comment letters, the toll of psoriasis is significant. With more than 50% of our community indicating that their psoriasis impacts their ability to enjoy life and 88% of individuals living with a family member with psoriasis reporting the same level of anxiety and depression as the person with the disease, it is important that individual patient perspectives be considered at all stages of this assessment.[4] We would note, though, that numerous items were missing from this one-page discussion of patient preferences and challenges including: fear of treatment failure, challenges with treatment utilization (beyond topicals) such as time and travel considerations required for administration (for infused therapies), challenges that come with trying to manage a chronic disease over a lifetime (including adolescents for which no biologics have a pediatric indication, during pregnancy, and during treatment for other disease and chronic conditions including cancer).

Omissions, treatments assumptions, and lack of real world administration considerations

The introduction of biologic products for the treatment of psoriasis and psoriatic arthritis has been the most significant advancement in care for the psoriasis community in recent decades. New systemic treatments, including biologics, have provided many patients with an effective therapy for the first time in their lives. In fact, today many people with psoriasis are able to achieve a level of clearance never before possible. Biologics have also opened up a new world of combination therapies, being used alongside systemic treatments, phototherapy and/or topical treatments. While these treatment types were discussed in the report, little mention is given to the use of multiple therapies in combination and is therefore not reflective of the real world use – and costs – of these therapies. This aspect of the assessment would have benefited from updated treatment guidelines which are currently under development by the American Academy of Dermatology and the National

Psoriasis Foundation, as well as a new paper entitled, "Treatment Targets for Plaque Psoriasis: U.S. Consensus" which will be published by the Journal of the American Academy of Dermatology in coming months.

When providing an overview of the immunomodulator treatment interventions, the treatment discussion of adverse events is too broad and lacks an appropriate level of context. In this section, ICER makes some generalizations and then singles out adverse events related to specific treatments inappropriately – such as listing only ustekinumab causes autoantibodies. Another example is the note that brodalumab may have "an increased risk of suicide," but without a black box warning yet for this therapy it is speculative for ICER to note the impact of this possible adverse event. Further, the report notes only that infliximab has an increased risk of infusion reactions without reference to the fact that one such reaction, anaphylaxis, though rare can lead to serious adverse consequences and even death.[5]

Another serious concern in this section of the report is the brief discussion given to (non-standard) dosing. By conducting the assessment with a rigid approach to dosing, which does not reflect the real world use and dosing adjustments to these therapies, the valuation of individual therapies is compromised. For example, the intervention table only details the possibility of a 300mg dose of secukinumab, without referring to a lower 150mg option that the report later notes is possible. The concerns here are similar to those we noted with discussions of etanercept, adalimumab, ustekinumab, and infliximab, all of which failed to note the possibility of patients needing to have the therapy administered more frequently than indicated by the label.

The NPF also noted that the report mentioned the FDA's approval of biosimilars for adalimumab (Amjevita®) and etanercept (Erelzi®) but did not include mention of the biosimilar for infliximab (Inflectra®) which was approved by the FDA in April 2016. Pfizer announced on October 17, 2016, that it plans to bring Inflectra to the market in the U.S. by the end of November.[6] Given the robust amount of activity in developing biosimilars to treat psoriasis and the number of approvals to date, it is surprising the report focuses so little on these developments, including their impact on pricing, prescribing, and patient and provider perspectives on use.

ICER cost model lacks transparency and acknowledgement of variability between payers and over time

Specialty drug spending – which includes spending on treatments for moderate to severe psoriasis and psoriatic arthritis – has been identified by several analyses as a driver of increased prescription spending. Given this, it is appropriate that we consider the value of everything from treatments to medical tests to system innovations. Nonetheless, efforts to open the Pandora's Box of drug pricing and assess value must be themselves transparent – describe costs used in the model, acknowledge and address variability between payers and over time, and ensure that comparisons are not conducted in an "apples to oranges" manner. The NPF was particularly challenged by the lack of a comprehensive description of the costs ICER used in the model. For example, ICER does not specify the "as of" date of the Truven Health Analytics Red Book® Online Wholesale Acquisition Costs (WACs) that are central to the cost analysis. The reader is left to impute, based on the access date for citation #111, that the date is August 2016. Given the variability in drug prices and the rapid increases of some psoriasis therapies[7], the date here is critical. *See Table 1.*

We also note that WAC costs (and all measures of drug costs) do not move in tandem for all drugs in a class; rather, price relativities change over time. *See Table 1.* The patents for adalimumab, etanercept, and infliximab are expiring (or have arguably expired) and all three are facing competition from biosimilars (with a biosimilar now approved by the FDA for each of these three therapies). The impact of these follow-on biosimilars on the short and long-term pricing and price relatives is currently unknown.[8, 9, 10, 11] Additionally, WAC is not the ultimate price paid by the

Table 1: Medicare Average Sales Price (ASP) Increase Q1 2015 to Q1 2016: As Reflected in Payment Allowance Limit Increases Q3 2015 to Q3 2016

Drug	One Year Increase
Adalimumab (20 MG)	25%
Etanercept (25 MG)	32%
Infliximab (10 MG)	7%
Ustekinumab (1 MG)	2%

Source: CMS, 2016 ASP Drug Pricing Files. Note: Medicare does not report ASPs for the other psoriasis drugs.

private or government insurance plans or the uninsured consumer and there are other measures of drug prices. For example, Red Book® Online, ICER's source for WAC, provides four other prices: average wholesale price (AWP), direct price (DP), suggested retail price (SRP), and federal upper limit (FUL).[12] Furthermore there are other proprietary drug price databases, including First Databank, Medi-Span, and Gold Standard that report their estimates of WAC and other prices.[13] It is arguable whether WAC and other wholesale price measures actually represent a wholesale price. [14]

Beyond these deficits in pricing assumptions within the report, it is well understood that different payers pay different prices (before rebates) and that little price transparency exists. Drug prices paid by commercial payers, including Medicare Part D prices, are negotiated,[15] often with the pharmacy benefit manager (PBM) as an intermediary.[16] Medicaid programs are the only payers for which some level of transparency exists, though even this realm is rather opaque. For example, while Medicaid prices are often legislated, the state-legislated prices are often based on AWPs or WACs from proprietary databases[17] and hence have a non-transparent element.

When rebates are factored in, the water becomes even murkier. Rebates are paid by drug companies after the purchase of the drug and are also often managed by the PBM. Rebates for commercial Medicare Advantage payers are sometimes in excess of 50% and are not consistent by drug or payer. Other than Medicaid, where rebates are established by federal regulation,[18] there is no rebate transparency and the only values generally available are estimates of average rebates.[19] Increased rebates may offset drug price increases for a particular drug so there is no net cost increase to a particular payer. Assuming one set rebate percentage, consistent across all therapies, fails to acknowledge the real and variable world of drug price rebates.

Further, the distinction between "medical" and "pharmacy" benefits is important for this assessment because some therapies, including the one recommended by ICER, fall in the medical category, meaning they are paid for under a very different model that includes other sizeable costs. However, ICER does not specify the laboratory and clinic visit costs, prices, or basis (payer and time) of the laboratory and clinic visit services included in the model when a medical product is used. Medical benefit drugs are billed (claimed) by a physician, clinic, or hospital outpatient department (using a "J" procedure code) rather than a pharmacy. J-code claims are paid by payers according to the contracts that the payer has with the physicians, clinics, or hospital outpatient departments – contracts in no way related to their PBM contracts. Medicare fee-for-service J-code payment prices are transparent and self-adjusting to market prices.[20] Medicaid J-code prices are often transparent, if one has the patience to research 50 state Medicaid plans, but are not necessarily related to market prices, and such prices might not apply to Medicaid managed care payers that are responsible for a significant and growing number of Medicaid lives. A Medicaid rule was finalized only this year that will allow Medicaid to collect rebates for infused drugs.[21]

Commercial insurance (including Medicare Advantage) J-code prices, however, are neither transparent nor necessarily related to market prices. Commercial prices may be based on a fixed "fee schedule" or a percentage of charges basis. Across provider-payer combinations, there is wide variation in J-code prices.[22] The rebate flow and magnitude is different for medical benefit drugs than pharmacy benefit drugs. It is also important to note that the PBM is not involved in the medical benefit drug purchase – the provider is the purchaser and any rebate is collected by the provider. While hospitals may have significant rebate arrangements, hospitals are paid according to their contracts with the payers, contracts that do not necessarily reflect either market prices or rebates.[23, 24]

From a patient standpoint, there are important differences between therapies that fall under medical versus pharmacy benefits. Medical claims are typically subject to deductibles and coinsurance rather than the copayments typical of pharmacy benefits. Patients often pay a significantly different percentage of payer-

allowed cost for a medical claim than a pharmacy claim, thus from the patient perspective cost is quite different. There is also a cost for infusion services and the costs vary substantially by payer and time. ICER estimates the cost for infliximab infusion services without providing a source for the estimate. Their cost is significantly lower than the cost (payer allowed amounts) reported by a study using 2006-2008 claims data of 72 medical clinics.[25]

Report findings and concerning one-size-fits-all recommendations

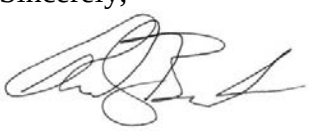
ICER concludes infliximab is the most cost-effective and highest economic value relative to the other drugs and targeted agents other than infliximab do not represent good value. The NPF is concerned about the number of omissions and assumptions that underlie these findings. Given the economic and clinical concerns raised above, this may, in fact, be wrong for some payers today or, if correct today, be incorrect in the near future. Additionally, such a one-size-fits-all determination does not account for the challenging nature of managing psoriatic disease or the challenges this course of treatment may impose upon patients (including missed time from work, availability of and travel time to infusion centers, and time for administration of the therapy). Infliximab, being a mouse molecule, has a higher rate of neutralizing auto-antibodies, which can lead to less efficacy and the need to increase the dose or switch drugs. The recommendation fails to appropriately address this need to increase dosing and frequency, nor does it address the high discontinuation rate associated with infliximab. ICER's conclusion that infliximab is the most cost-effective is also not consistent with other studies that have used health insurance claims data and found that infliximab has a similar or higher cost compared to other tumor necrosis factor (TNF)-blockers (although TNF-blocker use was not specific to psoriasis patients).[26, 27, 28] Additionally, the report fails to consider that methotrexate is sometimes given as an adjunct drug;[29] its frequency and costs should be included in the drug cost estimates. Likewise, topical drugs and UV treatments are often concomitant with drug therapy[30] and should be priced as part of the drug treatment.

Conclusion

As ICER moves toward the final report and New England CEPAC meeting, we acknowledge the benefit of bringing forward sound science and evidence that informs patients and providers about treatment options. No relationship in the health care landscape should be more sacred than that between the patient and provider. It is critical that patients and physicians have access to all of the therapies reviewed here – both new and those that have been on the market for more than a decade – along with those that come to market in the future. The extreme heterogeneity of this disease makes provider and patient access to the full range of therapies particularly important given that a treatment that may work for one may fail for another and because patients often cycle through a number of treatments during their lifetime. Only when physicians are able to access all the tools in their treatment toolbox will they be able to provide individual patients with the care that will maximize their health outcomes.

On behalf of National Psoriasis Foundation, thank you for your consideration of these comments which we hope will positively inform this review. We again invite you to call upon us, our Medical Board, and our patient community as you move forward. Please contact Leah Howard, JD, VP of Government Relations at lhoward@psoriasis.org with any questions.

Sincerely,



Randy Beranek
President & CEO

Cc: Abby Van Voorhees, M.D., Chair, National Psoriasis Foundation Medical Board

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Novartis appreciates the opportunity to provide feedback to ICER on its draft evidence report on treatment options for moderate-to-severe plaque psoriasis. We have provided key highlights and evidence on secukinumab that are not reflected in the draft evidence report.

Psoriasis, a lifelong systemic immune-mediated disease affecting approximately 7.5 million Americans, is a debilitating condition impacting patient well-being and quality of life.[1] Secukinumab, approved for the treatment of moderate to severe plaque psoriasis in adult patients,[2] is one of the most well-studied biologic treatments available for moderate to severe psoriatic disease. The development program included long term extension studies up to 5 years;[3] dedicated trials for hard-to-treat areas such as scalp, nail, and palmoplantar psoriasis,[4-6] which are highly burdensome for patients;[7-11] and head-to-head comparative trials against two different biologic treatments (etanercept and ustekinumab) over 52 weeks to demonstrate long-term comparative benefit.[12-14] ***The body of evidence supports the rapid, high level, and sustained efficacy and safety of secukinumab as an optimal therapy for patients suffering from moderate to severe plaque psoriasis, a lifelong disease. It is critical to understand and incorporate the full body of evidence when evaluating secukinumab in a value framework such as ICER's framework.***

Secukinumab is a fully human monoclonal antibody (mAB) that selectively binds to the interleukin-17A (IL-17A) cytokine and inhibits its interaction with the IL-17 receptor.[2] In the U.S., secukinumab is approved for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. Secukinumab is also approved for adult patients with active ankylosing spondylitis (AS) and psoriatic arthritis (PsA).[2] More than 10,000 patients have been treated with secukinumab in clinical trial settings across multiple indications, and over 50,000 patients have been treated in the post-marketing setting.[3] Findings from the large, available body of evidence support secukinumab's key profile benefits:

- **Long term sustained efficacy:** ***Secukinumab provides rapid and high level efficacy, including PASI 100, and is the only IL-17A antagonist with long-term sustained efficacy up to 4-years*** (PASI 75: 88.5***%***, PASI 90: 66.4%, PASI 100: 43.5***%)***.[15] Almost 100 % of PASI 90 and PASI 100 response rates are maintained from year 1 though year 4.[15] In addition, head-to-head trials with etanercept (PASI 75: 78.6% vs. 65.7%; PASI 90: 65.0% vs. 45.0%; PASI 100: 36.2% vs. 19.9%) and ustekinumab (PASI 75: 91.6% vs. 78.2%; PASI 90: 74.9% vs. 60.6%; PASI 100: 44.9% vs. 36.7%) up to 52 weeks have demonstrated secukinumab's sustained superior efficacy.[12,14] Although it is necessary to use short term outcomes to inform the cost effectiveness model due to clinical trial design, long-term evidence should be acknowledged and discussed. Lack of long-term efficacy evidence should be viewed as a limitation to other newer therapeutics.
- **Long term safety**: ***Secukinumab has a favorable safety profile and is consistent for up to four years, including low immunogenicity (<1%) & low injection site reactions (<1%).*** The most common adverse events (AEs) at Year 4 were nasopharyngitis (12.1%) and upper respiratory tract infection (3.5%) and were similar to those observed in Year 1.[15] These safety outcomes should be reflected in the *Long-term Adverse Events* section.
- **Recapture of response**: ***95% of secukinumab patients recaptured PASI 75 response within 12 weeks when re-treated following treatment withdrawal***. Unlike with infliximab, where patients can develop antibodies to the treatment during treatment interruption,[16] patients who have achieved good results (e.g., PASI 75) with secukinumab have a high probability of regaining their responses after treatment re-initiation.[17] This type of long-term efficacy and

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response is important in a chronic disease area, such as psoriasis, where treatment interruptions can occur for a number of reasons over the lifetime of the patient.

- **High level of efficacy in hard to treat areas**: Psoriasis patients with hard to treat areas such as palmoplantar, nail, and scalp psoriasis are known to suffer greater disability and discomfort than those with psoriasis on other areas.[9] ***Secukinumab is the only IL-17 that has studied these harder to treat patient populations in dedicated studies, and not as sub-analyses of phase 3 data.*** At Week 16, about 40% of patients achieved clear or almost clear palms and soles, a palmoplantar psoriasis investigator global assessment 0/1, with secukinumab 300 mg every 4 weeks, which continued to improve with approximately 60% of patients achieving clear or almost clear palms and soles at Week 80 (Year 1.5).[5] Secukinumab demonstrated superior efficacy at week 12 compared to placebo in moderate to severe scalp psoriasis (Psoriasis Scalp Severity Index (PSSI) 90 responses 52.9% vs 2.0%, respectively $p<0.001$).[4] Also, data from the nail psoriasis trial demonstrated improvement in nail psoriasis by over 60% on the Nail Psoriasis Severity Index at week 32 with secukinumab 300mg treatment.[6] ***ICER should include and quantify the value of effectively treating hard-to-treat areas.*** While the PASI ranges used in the ICER model help differentiate comparative efficacy, the PASI ranges assign equal weight to all affected areas and do not capture the quality of life differences. For example, the affected area is in an exposed location, such as the nails, hands, or feet, compared to a location that can be covered, such as the torso. Efficacy results are available by affected area as shown above for secukinumab and could be used to differentially weight the value of achieving PASI 75 or PASI 90 for that affected area. The ICER draft report does not address hard-to-treat areas. Minimally, the report should include evidence of efficacy on hard-to-treat areas, and ICER should consider including this differentiation in the model.
- **High efficacy in psoriatic arthritis patients**: Psoriatic arthritis is an inflammatory spondyloarthropathy frequently associated with psoriasis,[18] with approximately 10-20% of psoriasis patients eventually developing PsA.[19] ***Secukinumab is also approved for PsA and AS and demonstrated significant clinical responses in measures of joint symptoms (pain and swelling) as well as plaque psoriasis in patients with active PsA*** despite prior use of NSAIDs, corticosteroids and DMARDs. In FUTURE 2, 54% of secukinumab-treated patients achieved ACR20 compared with 15% placebo-treated patients. Further, significant improvements were also seen in enthesitis and dactylitis, which are also common symptoms of PsA.[20] ICER presents an incomplete picture of PsA efficacy in the draft report, only including evidence from secondary analyses of PsA patients. If ICER would like to address PsA in the report, all evidence on PsA should be presented, including the FUTURE 2 results.
- **Patient symptoms, quality of life improvement, and work productivity**: ***Secukinumab is the first dermatology product to have patient-reported outcomes data regarding symptom impact (pain, itching, scaling) in the product label***.[2] Secukinumab has demonstrated superior improvement in patient-reported symptoms, skin related quality of life (Dermatology Life Quality of Life Index), and work productivity than etanercept and ustekinumab.[12,21-23] Compared to ustekinumab, a significantly greater proportion of patients achieved complete relief of pain, itching, and scaling with secukinumab at week 52: 66% vs. 56%; itching, 46% vs. 38%; and scaling, 53% vs. 37% (all $p<0.05$).[21] Quality of life improvements with secukinumab are long-term with 71% of patients reporting a DLQI 0/1 response (indicating skin problems having no impact on patients' lives) at 4 years (starting at 73% in year 1).[15]

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Discussion of quality of life in the report should include patient-reported outcomes of symptom impact, consider time frames, and acknowledge long-term results.

Based on the data above and in an effort to further evolve the ICER value framework, additional suggestions specific to the report content are provided for your consideration below.

Comparative Clinical Effectiveness

ICER should use the 16-week primary endpoint efficacy results for the CLEAR trial. The CLEAR trial, comparing secukinumab directly to ustekinumab over a 52-week period, assessed its primary outcome at 16 weeks. Secukinumab achieved superior PASI 90 (79.0% vs 57.6%) and PASI 100 (44.3% vs 28.4%) than ustekinumab at week 16.[13] The PASI data provided in Table 6 in the draft report is from the CLEAR study; however, it is the 12-week, rather than the 16-week primary endpoint. Consistency should be applied by using the primary endpoint from clinical trials as it will impact the network meta-analysis (NMA) results for secukinumab.

The evidence ratings for available head-to-head comparisons should be revised and further explained. In Table 12 of the draft report, ICER provides evidence ratings for available head-to-head comparisons of the treatments under evaluation. The information contained within this table is critical to the report and its present format can easily lead to misinterpretation. Firstly, the term "head-to-head" in the table title is misleading and should be revised to "non-placebo comparisons" as it also contains NMA results. Secondly, the symbols for insufficient evidence on comparative net health benefit (I*) is too similar to the symbol for moderate certainty that net health benefit is comparable or inferior (I). These should be changed so that only one of them uses the letter "I." Lastly, the table key fails to explain that these results are to be interpreted as row vs. column. Having both results in a single cell might avoid misinterpretation of the results.

The rating for secukinumab vs. etanercept, ustekinumab, and adalimumab, should be raised to an A, A/B+, and B+, respectively.

- *Secukinumab vs etanercept.* The current B+ rating was given to secukinumab because there was only one head-to-head randomized controlled trial (RCT), compared to ixekizumab, which was rated an A (substantial net benefit) because it had two trials. Trial design should be also considered when making these ratings. The RCT comparing secukinumab to etanercept conserved randomization over a 52-week period, showing sustained superior efficacy over the long-term (vs. only for 12 weeks for both ixekizumab trials).[14] Since psoriasis is a chronic disease, long-term evidence should be valued more than short-term evidence (e.g., week 12). The rating for this comparison should be an A.
- *Secukinumab vs ustekinumab*. The current C+ rating was given because despite significant head-to-head evidence from the CLEAR trial both at weeks 16 and 52,[12,13] the NMA results do not corroborate a statistically significant difference. There are two primary reasons why this rating should be changed. First, the non-significant NMA results are dependent on the choice of NMA model. The difference is large when adjusting for placebo response with 55.3% of patients attaining PASI 90 for secukinumab relative to 33.3% for ustekinumab (Table G9 of the Draft Report). Second, the NMA only used short-term outcomes and did not account for any long-term evidence that might be currently available.[15] A large, well-designed RCT such as the CLEAR study over 52 weeks should remain at the top of the evidence hierarchy and as such, differences in short-term efficacy should not reduce the rating so severely. The rating for this comparison should be an A/B+.

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- *Secukinumab vs adalimumab*. The current I rating was given because the comparative efficacy was not statistically significant in the unadjusted NMA. However, both sensitivity analyses provided by ICER led to large differences in the proportion of patients attaining PASI 90: 55.3% for secukinumab vs. 31.7% for adalimumab when adjusting for placebo response (Table G9 in draft report appendix) and 52.9% for secukinumab vs. 31.6% for adalimumab when adjusting for ustekinumab dosing (Table G7 in draft report appendix). It is recognized that psoriasis populations have changed over time and that an unadjusted analysis is at-risk of bias. Thus, it is likely that this decision is based on choice of analysis rather than on the evidence itself. As such, given that the other analyses support improved comparative efficacy of secukinumab relative to adalimumab, there is evidence for a B+.

Evidence gaps

ICER should remove the inaccurate statement regarding concerns of infections and reactivation of latent tuberculosis (TB) for secukinumab. Kammüller et al 2016 conducted an analysis of data pooled from five randomized, double-blind, placebo-controlled, Phase 3 secukinumab studies in 2,044 patients: ERASURE, FIXTURE, FEATURE, JUNCTURE, and SCULPTURE.[24] Safety data on LTBI or active TB as an adverse event and treatment for LTBI were recorded. Across these five studies, zero cases of active TB infection were reported. In patients with a prior history of TB or who were diagnosed with LTBI at screening, there were zero cases of TB reactivation following treatment with secukinumab. The findings from these clinical trials are supported by results from both an *in vivo* mouse study which found no effect of anti-IL17 blockade on TB infection (vs anti-TNFα treatment which significantly increased bacterial burden) and pre-clinical *in vitro* testing which showed no reversal of TB dormancy following secukinumab treatment.[24] This finding is in accordance with zero TB infections reported in years 1-4.[15] The TB concerns statement for secukinumab should be removed from the evidence report. Secukinumab shows favorable safety profile in moderate to severe psoriasis through 4 years of treatment.[15]

ICER should review the pricing distribution applied to ustekinumab to accurately reflect current real-world usage. The costs in the report assume 70% of patients start on 45mg and 30% at 90mg based on clinical trial and older claims data; however, this is not reflective of real-world use of ustekinumab. A more reflective distribution of current treatment behavior based on 2015 data would be 52% at 45mg and 48% at 90 mg.[3] By using a dated utility distribution, the report reduces the relevance of its findings and risks underestimating the costs for ustekinumab, in turn biasing results of its value. ICER should review its costing for ustekinumab to ensure that the most up-to-date evidence reflecting real-world usage is used to inform any subsequent decision making.

ICER should better account for real-world usage of infliximab in the model. The ICER draft report finds infliximab to be the most cost-effective therapy evaluated. However, infliximab sees very limited real-world usage.[3] A recently published study using data from the Psoriasis Longitudinal Assessment and Registry (PSOLAR), a longitudinal psoriasis registry, found that of the 2,076 patients who started a new biologic during the registry, only 5.6% initiated on infliximab, compared to ustekinumab (50.1%), adalimumab (31.9%), and etanercept (12.4%).[25] The ICER report findings suggest that infliximab should be the preferred treatment, which is primarily reflective of cost, not physician prescribing patterns or likely patient preferences. Minimally, ICER should frame its findings in the context of real-world utility.

The ICER report should include key evidence findings for secukinumab on patient reported outcomes. Table 7 in the draft report contains DLQI outcomes across direct comparative trials,

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including the CLEAR trial comparing ustekinumab and secukinumab at week 16. Week 52 results are now available, with 71.6% of subjects on secukinumab vs 59.2% on ustekinumab ($p<0.001$) achieving a DLQI 0/1 response.[12] This new finding should be included in Table 7. These quality of life improvements reported by patients using secukinumab are durable with 71% of patients reporting a DLQI 0/1 response (indicating skin problems having no impact on patients' lives) at 4 years (73% in year 1).[15] At week 52, secukinumab was shown to lead to greater DLQI improvements than ustekinumab in all six DLQI subscales: symptoms and feelings -3.1 vs. -2.7; daily activities -2.6 vs. -2.3; leisure -2.2 vs. -1.9; work and school -0.8 vs. -0.7; personal relationships -1.7 vs. -1.4; treatment -1.1 vs. -0.9 (all $p<0.01$).[26] Secukinumab also demonstrated greater DLQI subscale response (score of 0) at week 52 vs. ustekinumab across all subscales: symptoms and feelings 52% vs. 41%; daily activities 83% vs. 74%; leisure 87% vs. 76%; work and school 87% vs. 76%; personal relationships 86% vs. 74%; treatment 88% vs 71% (all $p<0.01$).[26]

Below, we have included additional evidence findings on key patient reported outcomes included in the ICER report that missed secukinumab results. With the significant physical, social, and psychological burden imposed by psoriasis, patient-reported outcomes and other quality of life measures are particularly important to consider for psoriasis patients.[27]

- *Work Productivity:* Over 52 weeks, patients treated with secukinumab reported significantly greater reduction in work- and activity-related impairments (WPAI) from baseline, with similar mean baseline scores. Patients treated with secukinumab compared to patients treated with ustekinumab showed greater reduction in presenteeism -24% vs. -18%; work productivity loss -23% vs. -17%; and activity impairment -32% vs. -28% (all $p<0.01$).[23]
- *Sexual Function:* Secukinumab has demonstrated significantly improved responses on the DLQI subscale for personal relationships compared to ustekinumab. At week 52, 86% of patients reported no impact to personal relationships on secukinumab compared to 74% of patients on ustekinumab, with significant differences as early as week 4, ($p<0.01$).[28] On the DLQI item for *caused sexual difficulties*, secukinumab demonstrated improved responses with 89% of patients on secukinumab reporting no sexual difficulties at week 52 compared to 74% of ustekinumab patients, with significant differences as early as week 8, (all $p<0.01$).[28]
- *Symptom Control:* Moreover, secukinumab also demonstrated superior symptom relief based on patient assessment of psoriasis-related pain, itching, and scaling. The proportion of respondents at week 12 was significantly higher for secukinumab when compared with etanercept: pain 73% vs. 59%; itching 83% vs. 64%; scaling 83% vs. 59% (all $p<0.05$).[22] The proportion of patients achieving complete relief at week 12 was also significantly higher for secukinumab compared to etanercept: pain 59% vs. 35%; itching 44% vs. 25%; scaling 42% vs. 21% (all $p<0.05$).[22] At week 52, a significantly greater proportion of patients treated with secukinumab achieved complete relief of pain, itching, and scaling compared to patients treated with ustekinumab, with differences observed as early as week 4: psoriasis-related pain 66% vs. 56%; itching 46% vs. 38%; scaling 53% vs. 37% (all $p<0.05$).[21]

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October 20, 2016

Steven D. Pearson, MD, MSc, FRCP
President
Institute for Clinical and Economic Review
One State Street, Suite 1050
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RE: ICER Draft Evidence Report Psoriasis

Dear Dr. Pearson:

Patients Rising is a Washington, DC-based non-profit organization with a very specific mission: we advocate for access to vital therapies and services for all patients with life-threatening and chronic diseases. That is why Patients Rising is committed to bringing forward the patient voice as part of a balanced dialogue with providers, payers, policymakers and the advocacy community to address the complement of cost and access challenges Americans with serious diseases face every day.

One of the most pressing issues in health care today is the need to improve access to, and reimbursement for, precision and personalized medicines that enhance and extend people's lives. As an organization committed to educating patients on the important policy challenges affecting their care, we are in a unique position to closely observe and make direct comments to all of the frameworks ICER proposes.

Based on past comment letters, it goes without saying that we respectfully agree to disagree with the ICER's use of the QALY as a metric in determining the value of treatments. This is problematic for us because even though the end goal is to use it as an economic cost threshold the patient is given a value of less than one in the determination. This is an unfortunate casualty of the modeling and why we believe it should not be used in determining patient access.

Our first concern is -- where are the voting experts? An undisclosed number of consultations with a few experts, advocacy organizations and some patients does not adequately qualify the New England CEPAC voting panel to vote on the efficacy and cost provisions of these specific medicines that, if implemented, could affect the lives and quality of life of many psoriasis patients. At Patients Rising we would like to see more experts publicly brought into the voting process and not just listed at the top of a document as someone you had correspondence with without any context as to what that input included. With all due respect to the esteemed voting panel credentials, most of the members are not credentials I would want determining my access if I were a patient living with psoriasis.

In the age of personalized medicine, the choice to create topical reports limited in scope and generally focused on the most expensive -- sometimes yet to be released treatments – it begs the question, why? We are in an age of personalized medicine, and psoriasis is no different.

I will close with a story. Our friend Dave in Bethesda, Maryland has psoriatic arthritis. He was treated every six weeks and living a high quality of life, managing a restaurant and caring for his aging father. He had no side effects. He and his doctor were perfectly happy with his plan. But one day – out of nowhere – his insurance decided Dave now needs his treatment every eight weeks. His doctor has been fighting with his insurance company on Dave's behalf, even attempting to ask for an increase in his medication. So far, no luck.

But guess what? When Dave was treated every six weeks his pain was in check. He would get some minor aches a few days before treatment, maybe. But now he is in a low grade constant pain because the final two weeks he has to wait are so painful that the medication is no longer as effective.

No, Dave's problem is not the result of ICER's report. But Dave's problem is the result of insurance companies and bureaucratic entities practicing medicine for the doctors who are on the front lines with patients. Now Dave is no longer able to work as long, enjoy his down time and take care of his father in the same way he was on the treatment that worked for him.

How can we as a county raise the bar for patient care, when people like Dave are suffering unnecessarily? This is the result of impersonal guidelines like ICER's being implemented as a method to control costs without any firsthand knowledge of the patient. There must be a way to develop a framework that focuses on care concerns first because if we fail in focusing on the care, then we fail. There is no value added to a decision by creating a value cost framework missing all the nuances of true patient-centered care. We need a *value care framework* that obviously considers cost, but is created with physician experts and their patients at the forefront and voted on by a respected group of peers well versed in the treatment of the disease being reviewed.

Thank you in advance for considering our views.

Sincerely,

Terry M. Wilcox

Terry Wilcox
Co-Founder & Executive Director, Patients Rising

Society for Women's Health Research

October 13, 2016

Steven D. Pearson, MD, MSc, FRCP
Founder and President
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Two Liberty Square, Ninth Floor
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Dear Dr. Pearson:

On behalf of the Society for Women's Health Research (SWHR®), we appreciate the opportunity to comment on the Institute for Clinical and Economic Review's (ICER) draft evidence report titled "Targeted Immunomodulators for the Treatment of Moderate-to-Severe Plaque Psoriasis: Effectiveness and Value," in preparation for the meeting of the New England Comparative Effectiveness Public Advisory Council (CEPAC) in November.

SWHR, a national non-profit organization, located in Washington D.C., is widely recognized as the thought-leader in promoting research on biological differences in disease. For more than 25 years, our organization has brought attention to the variety of diseases and conditions that disproportionately or predominately impact women and is dedicated to transforming women's health through science, advocacy, and education.

Psoriasis is a chronic autoimmune disease, which can be difficult to treat due to the unpredictable manifestation of symptoms it can present and results in incorrect or delayed diagnoses and inadequate access to care. If the disease is not managed appropriately, patients suffer from excessive flaking and bleeding of their skin, which is sometimes accompanied by extreme pain, itching, and fatigue.

Approximately 7.5 million Americans are currently living with this chronic autoimmune disease. According to a 2015 National Psoriasis Foundation report, nearly 60 percent of women said psoriasis interferes with their capacity to enjoy life, compared to 52 percent of men. In addition, research shows that up to 30 percent of psoriasis sufferers may develop psoriatic arthritis, an inflammatory form of arthritis that can lead to irreversible joint damage if not treated.

Clinical research has resulted in several of innovative and effective therapies to treat this disease. These include: oral treatments, topical drugs, systemic medications, phototherapy, and biologics, which are prescribed for moderate to severe psoriasis and psoriatic arthritis that has not responded to other treatments. SWHR believes it is important for health care providers to have access to all of these treatment options since individual patients respond differently to medication therapies and treatments.

Society for Women's Health Research

As ICER finalizes its draft evidence report on psoriasis therapies, SWHR asks that you consider patients, especially women, who suffer from this disease and their need for effective treatment therapies that work for them. Thank you for the opportunity to provide comments on this draft evidence report. If you have any questions or would like to discuss this issue further, please contact me at heather@swhr.org or (202) 496-5003.

Sincerely,

Heather Boyd, MPP
Director of Public Policy
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