



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
Two Liberty Square, Ninth Floor
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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 therapies⁷, 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 AWP or WACs from proprietary databases¹⁷ 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 therapy³⁰ 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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- ¹ Lebwohl MG, Bachelez H, Barker J, et al. Patient perspectives in the management of psoriasis: results from the population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis Survey. *J Am Acad Dermatol*. 2014;70(5):871-881.e30. doi:10.1016/j.jaad.2013.12.018.
- ² Springate, D.A., Parisi, R., Kontopantelis, E., Reeves, D., Griffiths, C.E.M. and Ashcroft, D.M. (2016), Incidence, prevalence and mortality of patients with psoriasis: a UK population-based cohort study. *Br J Dermatol*. Accepted Author Manuscript. doi:10.1111/bjd.15021
- ³ Dalgard FJ, Gieler U, Tomas-Aragones L, Lien L, Poot F, Jemec GB, Misery L, Szabo C, Linder D, Sampogna F, Evers AW. The psychological burden of skin diseases: a cross-sectional multicenter study among dermatological out-patients in 13 European countries. *Journal of Investigative Dermatology*. 2015 Apr 1;135(4):984-91.
- ⁴ Martínez-García E, Arias-Santiago S, Valenzuela-Salas I, Garrido-Colmenero C, García-Mellado V, Buendía-Eisman A. Quality of life in persons living with psoriasis patients. *J Am Acad Dermatol*. 2014;71(2):302-307. doi:10.1016/j.jaad.2014.03.039.
- ⁵ Chávez-López MA, Delgado-Villafañá J, Gallaga A, Huerta-Yáñez G. Severe anaphylactic reaction during the second infusion of infliximab in a patient with psoriatic arthritis. *Allergol Immunopathol (Madr)*. 2005 Sep-Oct;33(5):291-2.
- ⁶ Pfizer Plans to Launch Remicade Biosimilar in November. <http://www.wsj.com/articles/pfizer-plans-to-launch-remicade-biosimilar-in-november-1476740161> October 17, 2016.
- ⁷ Reuters, Exclusive: Makers took big price increases on widely used U.S. drugs, April 5, 2016. Accessed October 17, 2016: <http://www.reuters.com/article/us-usa-healthcare-drugpricing-idUSKCN0X10TH>
- ⁸ The New York Times, [Makers of Humira and Enbrel Using New Drug Patents to Delay Generic Versions](#), July 15, 2016.
- ⁹ FTC Presentation, Sanford C. Bernstein, [Biosimilars: Commercial Perspective](#), February 4, 2014.
- ¹⁰ Wall Street Journal, [Knockoffs of Biotech Drugs Bring Paltry Savings](#), May 5, 2016.
- ¹¹ Pharmacy Times, [Biosimilar Competition: Perception and Reality](#), May 12, 2016.
- ¹² Truven Health Analytics, [Red Book Online Product Spotlight pdf](#), 2013.
- ¹³ U.S. Department of Veterans Affairs, [Determining the Cost of Pharmaceuticals for a Cost-Effectiveness Analysis](#), undated, accessed October 16, 2016.
- ¹⁴ Courthouse News Service, [Class Accuses Pharma Firms of Price Gouging](#), January 4, 2016.
- ¹⁵ U.S. Department of Veterans Affairs, *ibid*.
- ¹⁶ American Health Policy Institute, [The Prescription Drug Supply Chain “Black Box”: How it Works and Why You Should Care](#), 2015.
- ¹⁷ American Society of Health-System Professionals, [Medicaid Pharmacy Reimbursement Changes Coming Soon](#), March 11, 2016.
- ¹⁸ Medicaid.gov, [Medicaid Drug Rebate Program](#).
- ¹⁹ Bloomberg, [Decoding Big Pharma’s Secret Drug Pricing Practices](#), June 2016.
- ²⁰ CMS, 2016 [ASP Drug Pricing Files](#)
- ²¹ Medicaid.gov, [Covered Outpatient Drugs Final Rule with Comment \(CMS-2345-FC\) Fact Sheet, 2016](#).
- ²² Wong, et al, [Analysis of Drug and Administrative Costs Allowed by U.S. Private and Public Third-Party Payers for 3 Intravenous Biologic Agents for Rheumatoid Arthritis](#), *Journal of Managed Care Pharmacy*, 2011.
- ²³ Magellan Rx Management, Medical Pharmacy Trend Report, [Medical Benefit Product Referencing section](#), 2015.
- ²⁴ Drug Channels, [New Data: How Outrageous Hospital Markups Hike Drug Spending](#), 2016.
- ²⁵ Wong, *ibid*.
- ²⁶ Bonafede, et al, [Cost of tumor necrosis factor blockers per patient with rheumatoid arthritis in a multistate Medicaid population](#), *ClinicoEconomics and Outcomes Research*, 2014.
- ²⁷ Bonafede, et al, [Cost per Treated Patient for Etanercept, Adalimumab, and Infliximab Across Adult Indications: a Claims Analysis](#), *Advances in Therapy*, 2012.
- ²⁸ Gu, et al, [Claims Data Analysis of Dosing and Cost-of TNF Antagonists](#), *American Journal of Pharmacy Benefits*, 2010.
- ²⁹ National Psoriasis Foundation, [Systemic Medications for Psoriasis and Psoriatic Arthritis pdf](#), 2015.
- ³⁰ Foster, et al, [Patient Characteristics, Health Care Resource Utilization, and Costs Associated with Treatment-Regimen Failure with Biologics in the Treatment of Psoriasis](#), *Journal of Managed Care and Specialty Pharmacy*, 2016.