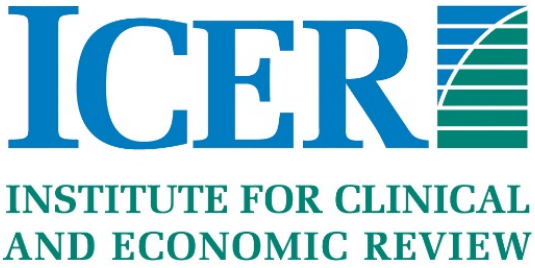

Dupilumab and Crisaborole for Atopic Dermatitis: Effectiveness and Value

Public Comments on Draft Report

May 12, 2017

Contents

OHSU

April 20, 2017

RE: Atopic Dermatitis Draft Evidence Report

Dear ICER Staff,

I am writing on behalf of the American Academy of Dermatology Atopic Dermatitis (AD) Expert Resource Group. We are a panel of dermatologists committed to advancing the care of patients with AD and we advise our Academy regarding important issues in the AD disease state. As healthcare providers, we view your Draft Evidence Report on AD recently published online as an important analysis with the potential to influence our care of patients on multiple levels. Thank you for the opportunity to provide feedback on the draft report.

The Topic in Context section captures the AD patient experience well. We are pleased the committee thoroughly reviewed the literature, treatment guidelines, and reached out to experts and patients to better understand available treatments. The section accurately reviews the burden this disease has on patients and families. Your clinical expert, Elaine Siegfried, succinctly summarizes the disease well in a recent New York Times article, "...atopic dermatitis doesn't kill you, it just ruins your life."

Regarding ICER conclusions describing net health benefit, we would argue that the comparative net health benefit of dupilumab over emollients is "superior" to emollients, not "incremental +" given the impressive reductions in disease severity (>70% reduction in sign scores), improvements in patient symptoms (>40% in itch), and statistical and clinically-relevant (i.e., meets MCID cut-offs) improvement in all other symptom scales, QOL scales, and mental health scales after 16 week of treatment. For those of us treating these patients in the clinic, dupilumab fills one of the biggest therapeutic gaps in all of dermatology. As a group, we all see patients suffering from severe itch and inflamed, cracked and painful skin for decades who have failed topical therapies. Many of these patients have received systemic steroids for far too long, many times with corresponding significant and permanent side effects affecting their skin, eyes, bones, and joints. While cyclosporine is an effective systemic therapy that many of our group prescribe, the vast majority of dermatologists do not prescribe it because of the known renal and organ specific toxicities and numerous drug interactions. These side effects also limit cyclosporine's duration of use. Methotrexate, mycophenolate, and azathioprine may be alternatives, but carry their own list of side effects and are not approved for AD.

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While the ICER health economics model for dupilumab falls within generally-accepted thresholds for cost-effectiveness, as treating clinicians we feel the therapeutic value of dupilumab is even greater than the model suggests. The additional benefits, not included in the model, include three areas: infection, comorbidities and cost of improper treatment.

Regarding infection: Aaron Drucker and colleagues performed a systematic review of skin infections in all dupilumab trials (published in abstract form) which showed a relative risk of 0.62 (95% CI 0.40-0.96) for the current FDA-approved dupilumab dosing schedule.[1] Skin infections are an ever-present problem for AD patients necessitating multiple antibiotic or antiviral courses. Skin infections often cause pain and flares of AD and may result in hospitalization. In addition to the concerns of drug-resistance, antibiotics come with a host of potential side effects. Another study by Narla and colleagues found adult patients with AD have a higher incidence of systemic infection, with some of these being related to skin.[2] Therefore, reducing skin infections may have broader implication on overall health.

Regarding comorbidities: The impact of dupilumab on the well-described comorbid atopic diseases, especially asthma, was not captured in your economic model. Up to 40% of patients with moderate-to-severe AD have concomitant asthma; thus a medication treating multiple conditions in the same patient provides higher value. Dupilumab is also being developed for other atopic diseases found more common in this population such as nasal polyposis and eosinophilic esophagitis.

Another comorbid condition dupilumab positively affects are mental health conditions. A statistically-significantly higher proportion of patients no longer met criteria for anxiety and depression after treatment with dupilumab in the SOLO 1 and 2 trials. As clinicians, we see the effect of the disease on patients' lives and the large burden of mental health disorders. A medication that can alleviate the symptoms of anxiety and depression improves the chances effective management for these mental health conditions while also minimizing he need for additional pharmacological intervention.

Also not captured in the health economic modelling are the side effects of poor adherence to standard treatments, the opportunity costs and risks of unproven alternative treatments and potential consequences of systemic corticosteroid overuse. With regards to systemic corticosteroids, this remains the most commonly used systemic therapy for AD. A recent study found that even in the patients who received proper systemic immunosuppressive therapy, >70% of them still have received systemic corticosteroids.[3] As you know, the effects of chronic systemic corticosteroids are numerous and many of them permanent. Poor adherence and use of unproven alternative treatments result from the need for complex and difficult regimens that yield slow and unsustained improvement. Alternatives to these existing options will provide significant cost-saving and other benefits not currently captured in your modelling.

In regards to crisaborole, your report states there is inadequate data to assess relative efficacy with topical calcineurin inhibitors (TCIs) and topical corticosteroids (TCS). From our perspective, crisaborole fills a gap we encounter daily in practice- the need for a safe, long-term and well-tolerated topical therapy for this chronic disease. Like the treatment of many complex and chronic diseases, the treatment of AD does not often lend itself to a perfect step-by-step approach. It is true, that for many patients, topical steroids are a cost-effective therapy that can be highly effective and safely utilized. However, because AD is a chronic disease, non-steroidal approaches are often needed for long-term

use or where topical steroids are ill advised such as the face, eyelids, and intertriginous areas like the groin and underarms. Although TCIs are labelled as "second-line" therapy, in reality they are less potent than many topical steroids. Thus they are incorporated most frequently as steroid-sparing agents and for the treatment of areas of the body susceptible to steroid side effects. As noted by your report, TCIs have a black box warning and frequently cause burning upon application. This local adverse reaction may become intolerable and lead to drug discontinuation. Thus, dermatologists have been in need of additional non-steroidal options to have in their arsenal for these clinical situations. While relative efficacy of crisaborole is an important question that needs answering, the relative efficacy is less important to our group than the ability to use a well-tolerated and effective therapy within a topical treatment regimen individualized for each patient to achieve the best and safest outcomes.

In summary, the AAD AD Expert Resource Group recognizes the need to practice medicine that is cost-effective and high in value. Until recently, patients with AD of all severities have had limited options that are safe and effective over the long-term. In fact, many patients and providers resorted to regimens that either inadequately treat the disease or lead to permanent side effects. The addition of both dupilumab and crisaborole to our pharmaceutical armamentarium provides patients the opportunity for effective, safe and individualized care that provides value to our patients and to the field beyond what can be captured in traditional economic modelling.

Sincerely,

Eric L. Simpson, MD, MCR
Chair, Atopic Dermatitis Expert Resource Group for the American Academy of Dermatology
Professor, Dermatology

And additional AD ERG Members:

David Cohen, MD, MPH, New York University Langone Medical Center
Robert Silverman, MD, Georgetown University Medical Center
Amy S. Paller, MD, Northwestern University Feinberg School of Medicine
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Jon M. Hanifin, MD, Oregon Health & Science University
Julie Block, President and CEO, National Eczema Association
Wynnis Tom, MD, University of California, San Diego

1. Drucker A, et al. Risk of skin infections with dupilumab for atopic dermatitis: Systematic review and meta-analysis of randomized controlled trials. Poster 282. J Invest Derm Supp. Volume 137 Number 5S, Supplement 1, May 2017

2. Narla S, et al. Atopic dermatitis is associated with increased risk of serious infections in US children and adults. Poster 223. J Invest Derm Supp. Volume 137 Number 5S, Supplement 1, May 2017

3. Armstrong AW, et al. Real-world utilization patterns of systemic immunosuppressants among US adult patients with atopic dermatitis. American Academy of Dermatology Annual Meeting 2017, Poster 5523

April 17, 2017

Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Subject: ICER Draft Evidence Report for Crisaborole and Dupilumab

The International Eczema Council ("IEC"), the largest global organization of dermatologist experts on Atopic Dermatitis, welcomes the opportunity to comment on the draft evidence report for Crisaborole and Dupilumab published on March 24, 2017. As physicians from more than 20 countries dedicated to increasing the understanding of AD and promoting its optimal management through research, education and patient/family care, we appreciated the comprehensive nature of your review and report. We would like to highlight the complexities and concerns related to the burden and comorbidities of AD as well as the high unmet need for both safe and effective topical and systemic, long-term treatments.

As noted in your report, atopic dermatitis/ atopic eczema is an extremely common disease affecting an estimated 30 million patients in the US alone. Its symptoms and extensive comorbidities result in a tremendous burden on patients and society in terms quality of life, social, academic, and many other consequences. The physical aspects of the disease include not only itching and scratching, but also sleep, pain, bleeding and dietary limitations. Patients with AD suffer from tremendous emotional consequences such as behavioral problems, irritability, crying, and social isolation. The adverse impacts on QoL extend to the adults who devote significant amounts of time to caring for children with AD. From an economic perspective, the cost of AD on patients and society for both direct costs, such as prescriptions, physician visits, and emergency and hospital costs, as well as indirect costs including decreased productivity and absenteeism, are overwhelming and have been estimated at over $4 billion.

From a treatment perspective, much of the management of the disease currently falls upon the patient and family to maintain a rigorous, time-consuming skin care regimen. Furthermore, some of the more common and effective treatments, such as topical corticosteroids, carry with them the potential of local side effects and unlikely systemic side effects which have, nevertheless, resulted in "steroid phobia" among patients, family and even physicians. In addition, the stigma of a black box warning for the hypothetical risk of cancer (which has yet to materialize) for the only previously available topical steroid alternative, the topical calcineurin inhibitors (TCIs), has also led to concern about use and has limited the effectiveness of TCIs as a viable treatment alternative. Given these issues, a vast number of patients with mild-to-moderate AD remain inadequately treated or untreated. Crisaborole is the only effective topical agent that does not have a

theoretical or established side effect profile that would limit its use. There currently are no other non-steroidal treatments available to help fill the void.

Regarding dupilumab and advancing systemic therapies, it is important to note the recent evidence of overt systemic immune activation in blood of patients with AD, leading to significant abnormalities in the non-lesional skin of patients with moderate to severe disease and also contributing to the growing list of comorbid disorders associated with AD. These data also highlight the importance of long-term disease control with systemic treatments that are safe for long-term use and are able to reduce not only the disease manifestations but also the risk of systemic comorbidities, including life-threatening diseases. These comorbidities include more frequent and severe bacterial and viral infections, as well as the "atopic march" of AD to other atopic disorders such as asthma and food allergies. Recent evidence also suggests linkages of AD ranging from depression, anxiety, and suicidal ideation to obesity, cardiovascular disease and lymphoma.

However, the available systemic treatments have serious drawbacks and side effects and are not suitable for long term use. Phototherapy has limited effectiveness, and the time commitment required for phototherapy is impractical for most patients. Systemic corticosteroids, while effective, have significant side effect risks and often result in severe rebound upon discontinuation. Cyclosporine, an immune suppressant which has been widely used in AD patients has been shown to have permanent effects on the kidneys by 1 year of continuous use, and cannot be given long-term. Other immune suppressants are less effective than oral steroids and cyclosporine, but have their own serious potential risks. Given the lack of safe and effective systemic treatments, a significant number of AD sufferers essentially remain untreated. Dupilumab is the first targeted, long-term therapy available for these patients which to date has demonstrated high efficacy and equally important has demonstrated very good safety for long-term use.

We appreciate your recognition that AD "is a disease that is frequently undertreated, and for many patients, is lacking treatments," and we're greatly encouraged that after 15 years without any therapeutic advances, we're beginning to see the emergence of new and promising treatments. We're further encouraged to see the parallels in the evolution of research and treatments for AD and for psoriasis ten years ago when the development of targeted treatments led to a transformation in care for psoriasis patients. We welcome the opportunity to continue the dialogue with you at this crucial period for AD.

Sincerely,

Amy S. Paller, MD, MSc
President, IEC

Emma Guttman-Yassky, MD, PhD
President-Elect, IEC

April 17, 2017

Submitted electronically to: publiccomments@icer-review.org

Steven D. Pearson, MD, President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Re: Feedback on ICER's Dupilumab and Crisaborole for Atopic Dermatitis: Effectiveness and Value 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 regarding the cost-effectiveness of dupilumab and crisaborole for treating atopic dermatitis.

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 more than 800 physician advocates committed to patient access. IfPA is a 501(c)(3) public charity non-profit organization.

Feedback on Draft Report

The ICER report correctly emphasizes many of the health problems associated with atopic dermatitis, however, several methodological assumptions and decisions that were made in producing the report raise concerns from a patient perspective.

1. "Data availability challenges" leave the report's impact on patients in question.

To begin, we have concerns regarding the timing of the ICER report. Throughout the study, the authors insert a caveat about significant "data availability challenges," particularly for dupilumab. This caveat was necessary because dupilumab was not available for purchase by patients when the draft analysis was being conducted. It is likely that the lack of data availability has meaningfully impacted the results of the analysis.

For instance, since dupilumab was not yet available on the market, the price of the drug is unknown. The ICER report assumes that the drug will cost $30,000, and then performs a sensitivity analysis around this value. Such an assumption may be accurate, but it may be inaccurate.

Therefore, the analysis presents a hypothetical result that may, or may not, be applicable to dupilumab depending upon its final price. Yet the ICER methodology creates a cost-effectiveness value with an implied precision that is clearly inappropriate for a drug that has not yet been sold on the market. Moreover, the impact of this report on patient access if dupilumab either assumes a higher initial price, or rises over time to reach a higher price, than $30,000 remains unclear.

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2. "Data availability challenges" on long-term impact undermine dupilimab's net health benefit grade.

Similarly, an important input into ICER's cost effectiveness analyses is the long-run health impacts from the drug under evaluation. These impacts are unavailable for dupilumab, which leads to arbitrary ratings in the ICER report.

For example, with respect to clinical effectiveness of dupilumab, the ICER report states:

> *"For adults with moderate-to-severe atopic dermatitis inadequately controlled with topical therapy, or for whom topical therapies are medically inadvisable, we have high certainty that dupilumab provides at least a small net health benefit ("B+") relative to treatment with emollients with or without continued failed topical treatments. Given limitations of the evidence base, most notably the lack of long-term evidence on the safety of dupilumab, we have moderate certainty that the net health benefit of dupilumab is comparable or better than that provided by cyclosporine, but we have high certainty that dupilumab does not produce a lower net health benefit. Our comparative clinical effectiveness rating for dupilumab versus cyclosporine is therefore "C+"."*

Put differently, the drug is new, therefore, no one has taken it long-term. Since there is no data on long-term impacts, the authors decided that a one letter-grade decrease in the clinical effectiveness of dupilumab was appropriate. The report provides no methodological reason why a one letter-grade decrease is a justifiable penalty. The reduction appears arbitrary at best.

More broadly, and as the above quote indicates, the novelty of dupilumab means that, by definition, the long-run impacts for patients are unknown. Perhaps these long-run impacts are positive – the drug will be well tolerated by patients with few side effects. In such a case, it may have been more appropriate to give dupilumab a one letter grade increase, not a decrease.

Or, perhaps these long-run impacts are negative – the drug will not be well tolerated by patients, or there will be many potential side effects – and a downgrade is appropriate after all. But, even here, whether that should be less, or more, than one letter grade is simply unknowable at this point. In fact, such considerations are precisely why the FDA requires continued drug monitoring of novel therapies after they have been released onto the market.

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3. Inattention to subjective factors such as quality of life benefits artificially deflates the value of these therapies to patients with atopic dermatitis.

The ICER report lists several non-medical or non-quantifiable medical benefits to patients who are able to control the symptoms and consequences of atopic dermatitis. These include: unmeasured patient health benefits, impacts on productivity, impact on caregiver burden, impact on public health, lifetime burden from illness, lack of availability of a treatment previously, and interpersonal burdens.

Overall, these benefits represent quality of life improvements that occur when patients can effectively manage their atopic dermatitis. Despite these important benefits, the ICER report then proceeds to declare: "The model used a US health system perspective (i.e., focus on direct medical care costs only)."

The ICER report likely takes this route because "quality of life" factors are difficult to quantify; the report states as much. Yet the omission of these factors will, by definition, artificially lower the benefits that the ICER report expects dupilumab to provide.

Quality of life considerations are always important from a patient perspective; however, such considerations are even more important for diseases such as atopic dermatitis. Many of the condition's quality of life impacts, such as adverse mental health impacts, physical discomfort, or adverse social impacts, are difficult to quantify. In fact, even diagnosing the severity of atopic dermatitis as mild, moderate, or severe can require subjective considerations. To patients suffering from this disease, however, these subjective assessments are incredibly important.

Therefore, while it is always a mistake to judge the cost-effectiveness of a drug solely on its impact on direct medical costs, the costs from this mistake are compounded for atopic dermatitis. With respect to the ICER report, the omission of these other factors from the cost-effectiveness assessment surely means that the estimated benefits in their model are conservative at best, and more likely to be inappropriately low for most patients.

These benefit impacts are particularly important because, based on the assumed price of $30,000, dupilumab meets ICER's typical QALY cost thresholds. Therefore, if the assumed price is correct, then the value of dupilumab is much greater than ICER is acknowledging. Consequently, it is vital that the ICER report incorporate reasonable estimates of these subjective costs.

Many behavioral economic studies provide methodologies designed to create cost proxies for subjective assessments. While applying these methodologies will be difficult, and

care must be taken to ensure a correct estimate is used, ignoring the costs from subjective benefits create a serious bias against any medicine that is developed to address diseases with harder-to-quantify impacts.

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4. Value estimates based on pricing assumptions and incomplete data could ultimately undermine access to treatment for patients with atopic dermatitis.

To the extent that health plans use cost-effectiveness data to determine how accessible a treatment will be for patients, ICER's determination that dupilumab and crisaborole are cost effective may bode well for atopic dermatitis patients' ability to access treatment. That access retains an element of uncertainty, however, because of the tentative nature of the data used in calculating the therapies' value – in particular, the cost and long-term effectiveness of dupilumab.

Consider patients who may soon begin receiving and benefitting from dupilumab for their atopic dermatitis. Should the treatment's price rise above ICER's estimate, will health plan coverage for the treatment dissipate? Likewise, if long-term impact data becomes available and drives down ICER's net health benefit grade, already artificially low, will the new data negate the therapy's calculated cost effectiveness, jeopardizing health plan coverage?

Tentative findings are vulnerable to reversal, leaving patients who find stable treatment with dupilumab at risk of later losing access or facing non-medical switching attempts by their health plans.

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Conclusions

For the above reasons, we have reservations regarding how the ICER report may impact patient access to appropriate treatment for atopic dermatitis. We encourage ICER to revisit the seemingly arbitrary reduction in net health benefit assigned to dupilumab and to also consider how to better incorporate subjective factors related to patient quality of life into its final report.

If IfPA can provide further detail or aid the Institute for Clinical and Economic Review in incorporating any of the above recommendations into its final draft, please contact us at 202-499-4114.

Sincerely,

Brian Kennedy
Executive Director

April 20, 2017

Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

To Whom It May Concern:

On behalf of the National Eczema Association (NEA), the Asthma and Allergy Foundation of America (AAFA) and the millions of patients we serve, we thank you for your thorough evaluation of the clinical efficacy and cost-effectiveness of dupilumab and crisaborole for the treatment of atopic dermatitis (AD).

Dupilimab and crisaborole are the first drugs approved for atopic dermatitis (AD) in 16 years. These approvals mark the beginning of what we believe will be a steady stream of new medications for this chronic, inflammatory disease. We recognize that ICER's evaluation influences patient access to medications and may affect future research and development of drugs for atopic dermatitis. Therefore, ICER's final evaluation of dupilumab and crisaborole are critically important to us as advocacy organizations and to our patient community.

What follows herein are points of emphasis and agreement, comments, questions, and considerations that may enhance your final report and better serve your stakeholders.

We agree with the report's conclusion that many of the burdens AD patients and their families endure are difficult to measure objectively. AD is a complex disease and its impact on patients' and their families' lives is complex and multi-dimensional. AD symptoms like itch, rash and pain are measured and documented in clinical studies. However, the impact of these symptoms on mental health, social function, work and school absenteeism and presenteeism, the time required for daily treatment, and direct and indirect medical costs for that care – remains largely uncaptured. Though there is much more work to do to document AD's impact on quality

of life (QOL), exisiting studies suggest that AD is one of the most debilitating dermatological conditions, with patients consistently reporting higher DLQI scores than psoriasis patients.[1]

To address this lack of robust QOL data, ICER contacted NEA and AAFA to gain perspective on value and identify outcomes important to patients. Subsequently, ICER staff held a listening session with a patient to understand the effect of AD on her life; reviewed primary QOL and treatment satisfaction data submitted by NEA; and sought referrals from NEA and AAFA to clinical experts who could help identify important QOL measures. We are pleased that ICER took every reasonable step to identify and quantify the impact of AD on patient quality of life.

We also acknowledge the ingenuity of ICER to reflect the impact that AD has on patients' lives in various states of severity by using quality-of-life scores as a proxy for patient utility in the cost-benefit section of its evaluation. ICER uses the delta in EQ5D scores as a means of measuring how dupilumab and its comparitor affected patients' quality of life pre- and post-treatment. We believe that this was an appropriate approach given the paucity of cost data available.

It is unfortunate that the effectiveness of dupilumab for treating comorbidities, like asthma, was not captured in the ICER cost-benefit analysis. As the report concedes, "the overall benefit to quality of life of treating patients with dupilumab who also have other atopic diseases, such as asthma and nasal polyposis, should have been captured in [the] analyses." The reason given in the report for not considering the cost offsets is a lack of data on the potential benefits of stopping other expensive therapies used to treat them. This is unfortunate. Dupilumab's potential efficacy in treating atopic comorbidities could yield significant cost savings. These savings may positively affect dupilumab's value estimate and provide a more accurate picture of its cost-effectiveness.

We would appreciate a clearer, more detailed, description of the ICER process used to develop cost estimates. For example, it would be useful to know if direct costs due to hospitalization can be linked to known AD comorbidities such as infection.

The final report would benefit from incorporating a broader spectrum of benefits and costs than what are captured in most clinical studies and cost-benefit analyses. NEA and AAFA believe that AD patients and providers should have access to the broadest range of effective treatment options possible. Crisaborole has advantages that distinguish it from other existing topical treatments for AD, especially with regards to side effects and long-term use.

Crisaborole can be applied generally to patients' bodies including face and eyelids, does not cause the sensation of pain except in 4.6 percent of patients, and has not been demonstrated to have the risks of long-term use associated with topical steroids, like thinning of the skin. It does not have a "black-box warning," like topical calcineurin inhibitors (TCIs) nor does it elicit the fearful reaction that topical steroids do in patients. Patient concerns with TCIs and topical steroids, real or imagined, decreases their willingness to adhere to recommended protocols and,

[1] LUNDBERG, JOHANNESSON, SILVERDAHL, HERMANSSON, and LINDBERG, *Health-related Quality of Life in Patients with Psoriasis and Atopic Dermatitis Measured with SF-36, DLQI and a Subjective Measure of Disease Activity*, Acta Derm Venereol 2000; 80: 430-434

thereby; the actual effectiveness of these drugs. These aspects of crisaborole's application are clinically relevant, important to patients and providers, and should also be considered by the committee.

In summary, we appreciate the work by ICER to solicit the patient perspective in its evaluation of dupilumab's and crisaborole's clinical and cost-effectiveness. We look forward to working with ICER to address some of the challenges outlined here, as we believe these issues are relevant in future studies of AD drugs, and to ensure that AD patients' needs are represented as completely and accurately as possible. Thank you again for proactively reaching out to us.

Respectfully,

Julie Block
President and CEO
National Eczema Association

Lawrence B. Schwartz, M.D., Ph.D.
Director, Board of Directors
Asthma and Allergy Foundation of America

PATIENTS FOR
AFFORDABLE DRUGS™

TO: Institute for Clinical and Economic Review

FROM: David Mitchell
Patients For Affordable Drugs

RE: Atopic Dermatitis and ICER Review Process

DATE: April 21, 2017

Background

My name is David Mitchell. I am the co-Founder and President of Patients For Affordable Drugs. We are the only national patient organization focused exclusively on policies to lower the price of prescription drugs. We do not accept funding from any organizations that profit from the development or distribution of prescription drugs.

More importantly, I have an incurable blood cancer called multiple myeloma. Most Tuesdays recently, I have received five hours of infusion with a two-drug combination priced at $20,000. I will receive this treatment 22 times over the course of a year. That means my drugs cost $440,000 per year – just to stay alive. I am grateful for these drugs and I am lucky to have a quality Medicare supplement policy. But millions of Americans are not so fortunate.

In just eight weeks, Patients For Affordable Drugs has collected over 5,000 stories from Americans struggling to afford prescription drugs. The cries for help come from every region, walk of life, and political affiliation in our country. One woman from Maryland wrote, *"Sometimes I have to decide to pay bills, eat, or get the prescription drugs I need to live."*

It is wrong. High drug prices hurt patients. And it must change.

Value-Based Pricing and ICER Process

Right now, prescription drugs are priced without regard to the value they deliver to patients. Instead, corporations price their drugs based on maximizing profits. Value-based pricing for prescription drugs holds great promise as a new framework that can move us away from pricing based only on the market power of drug corporations. We believe value should be the starting point for negotiations with government, employers, insurers, and other payers.

The work of the Institute for Clinical and Economic Review (ICER) can be foundational to the creation of a new system to ensure that patients have access to drugs they need and that those drugs are affordable and fairly priced. We applaud ICER for its work and for its inclusive and

responsive process which engages patients like me, listens to concerns, and takes into account our real world experience. Value frameworks will only deliver on their promise if they are built around the needs and experiences of patients.

It is unfortunate that some groups claiming to represent the best interests of patients disseminate false information and aim to scare patients by asserting that efforts to align prices with value will hurt patients' access to drugs. The fact is that patients are already being hurt by high prices. Thirty percent of cancer patients go bankrupt. Ten percent of patients with my disease report that they stop taking their drugs because they are too expensive.

Input from certain patient groups must be scrutinized in light of their funding. *The New England Journal of Medicine* recently reported that 83 percent of patient groups in the U.S. receive funding from pharma. *The New York Times* has documented the chilling effect that pharma-funding can have on patient groups' positions on pricing. Sadly, there are groups that go further and attack ICER's steps to curb unfair prices. Many of these groups represent drug corporations over patients. We hope that ICER will not be influenced by groups that are funded by and operate on behalf of drug corporations.

Atopic Dermatitis

We are not experts on Atopic Dermatitis and will not offer specific comments on the ICER review. However, we are pleased to note that Regeneron recently brought a new drug to market—Dupixent—after considering value and consulting with ICER. The price of $37,000—while very expensive and out of reach for many families—is below alternative treatments. We believe the decision of Regeneron to consider value is a step in the right direction, and we believe this demonstrates a move toward value pricing. We encourage ICER to continue it's work that will help hold down prices.

Pfizer Inc
235 East 42nd Street
New York, NY 10017

April 21, 2017

Steven D. Pearson, MD, MSc
President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109
Submitted via email: publiccomments@icer-review.org

RE: Comments on Draft Evidence Report for Atopic Dermatitis

Dear Dr. Pearson,

On behalf of my colleagues at Pfizer Inc, I am writing in response to the Institute for Clinical and Economic Review's (ICER) release of the draft evidence report titled "Dupilumab and Crisaborole for Atopic Dermatitis: Effectiveness and Value".[1]

We appreciate ICER's efforts to seek input from a broad range of stakeholders. Life sciences companies like Pfizer devote significant resources to research, and our scientists have developed deep expertise in understanding the clinical, economic, and quality of life impacts of inflammatory conditions like atopic dermatitis (AD).

Our colleagues have carefully reviewed the draft evidence report, and would like to offer the following comment and suggestions, particularly as they relate to ICER's review of the clinical evidence related to crisaborole:

Concern #1: Validity of comparative data generated by ICER

On page 33 of the draft report, ICER notes a lack of study data comparing crisaborole to active treatment. ICER then details its efforts to generate comparative data by using two studies comparing pimecrolimus to placebo. The authors of the report acknowledge that the two pimecrolimus studies use 6 point static Investigator Global Assessment (IGA) scales, while the two crisaborole trials utilized a 5 point static IGA scale. The authors then proceed to make comparisons across the studies, noting that because "the severity of disease in the trials appeared to be reasonably similar with regard to baseline IGA score and percent body surface area involved", the authors felt comfortable undertaking "indirect comparisons using Bayesian network meta-analyses (NMAs), assuming "clear" and "almost clear" categories are similar on both scales".

We disagree with ICER's assessment that the perceived similarities in baseline trial populations and IGA response scale structures allows for comparisons to be made across trials. While the discipline of meta-analysis offers powerful statistical tools that can help make comparisons across clinical trials, the results of any meta-analysis are directly a function of the assumptions made. We ask that ICER strengthen its report by offering a stronger rationale for the comparability of the crisaborole and pimecrolimus trial populations. Was the comparability of trials discussed with clinical experts? Did ICER consider what important

[1] Institute for Clinical and Economic Review. Dupilumab and Crisaborole for Atopic Dermatitis: Effectiveness and Value. Draft Evidence Report. Available at: https://icer-review.org/wp-content/uploads/2016/10/WCEPAC_Atopic_Dermatitis_Draft_Evidence_Report_032417.pdf. Accessed on April 12, 2017.

differences there were in clinical trial design, such as potential differences in the pimecrolimus vehicles between trials, or formulations used in the two studies?

We further ask that ICER offer a stronger rationale for the comparison of the 5 versus 6 point scales used in the crisaborole and pimecrolimus trials, respectively. In the report, ICER offers no scientific rationale for the comparison of "clear" and "almost clear" categories on both scales. We recommend that ICER articulate the reliability and validity of this comparison in detail before publishing the final report.

We also ask that ICER include additional background regarding the limitations and adverse effects associated with topical therapies. On page 35 of the report, ICER notes that adverse events with crisaborole were rare. However, safety events were not reported for the other topical agents considered, except for a brief a statement "that concerns about the safety of other topical agents may be greater than is warranted". We disagree with that statement, as side effects and limitations of use are well documented for the topical agents considered.[2] For example: continuous use of topical steroids for long periods of time are not recommended, and use on thin skin areas should be limited. Similarly, use of topical calcineurin inhibitors is recommended only for short term and non-continuous chronic treatment, and safety concerns have led to the issuance of a black box warning label from the Food and Drug Administration.[2]

Concern #2: Potentially misleading statements made by ICER re: its comparative efficacy findings

On page 34 of the report, in discussing the limitations of the crisaborole network meta-analysis, the authors acknowledge that their approach to the pimecrolimus comparison is limited, noting that:

> *In addition to statistical uncertainty, the trials were performed in very different time periods and used different versions of static IGA scales. Also, there are concerns that the pimecrolimus comparator vehicle can be irritating, and so the relative effects of pimecrolimus versus vehicle may appear greater than the relative effects of crisaborole which was compared to a less irritating vehicle. Given the uncertainties, we cannot come to firm conclusions about the relative efficacy of crisaborole and pimecrolimus. Pimecrolimus appears to be less effective than tacrolimus or moderate potency topical corticosteroids.*

Yet on page 36, in summarizing the findings from the meta-analysis, ICER states that "Despite this uncertainty, given the results of a network meta-analysis, *crisaborole appeared unlikely to be as efficacious as higher potency topical corticosteroids or 0.1% tacrolimus*" [emphasis added]. This contrasting statement is especially troubling given that the only reference to tacrolimus in the clinical efficacy review is a brief sentence (which appears at the end of the block quote above), citing, but not reviewing, a Cochrane study of pimecrolimus.

Even with the caveat of "uncertainty" raised above, ICER's comment regarding the relative efficacy of crisaborole compared to other treatments is clearly overstated and misleading to readers who may not have the scientific basis to understand the limitations of ICER's approach. We ask that ICER replace its statements regarding the relative efficacy of crisaborole with more factual language that simply acknowledges that comparative analyses are currently not possible given the lack of data at this time.

Further, in reading the report we note that there are a number of sentences that we believe misrepresent the state of the evidence and / or data available related to crisaborole. Given that they are not based in fact, such statements significantly reduce the scientific value of ICER's approach and findings and thus could confuse readers. These include (but are not limited to):

- Broad statements made without scientific backing, such as:

[2] Ring, J., Möhrenschlager, M. & Henkel, V. Drug-Safety (2008) 31: 185. doi:10.2165/00002018-200831030-00001

- "Mild-to-moderate disease *can often be effectively controlled with existing topical therapies*, but concerns about the side effects of those therapies inhibit treatment in many patients" (page 12, emphasis added).
  - ICER presents no scientific data supporting the statement that mild or moderate disease can be effectively controlled with existing therapies.

- "Trials of crisaborole also did not assess effects on productivity, but crisaborole is used in patients with mild-to-moderate atopic dermatitis where *productivity effects are likely to be less pronounced*" (page 37, emphasis added).
  - ICER presents no evidence that productivity issues are less pronounced in this population, and there are studies that suggest that there may be significant indirect impacts of AD on families.[3][4]

- Specific statements which belie the statistical significance (or lack thereof) of findings:
  - "The improvement rate was *moderately higher* in the crisaborole arm than in the placebo arm for each individual atopic dermatitis sign evaluated, including erythema (59% vs. 40%; p<0.001), exudation (40% vs. 30%; p<0.001), excoriation (60% vs. 48%; p<0.001), induration/papulation (55% vs. 48%; p=0.008), and lichenification (52% vs. 41%; p<0.001)" (page 33, emphasis added).
    - ICER's statement that improvement rates are "moderately higher" does not reflect the statistical significance of the findings; the qualitative statement is not applicable.

  - "There was a *trend suggesting pimecrolimus was superior* to crisaborole" (page 34, emphasis added).
    - ICER's statement regarding this "trend" does not acknowledge the actual lack of statistical significance in its findings.

- Statements made referencing commentary from unidentified "experts" that are not supported by other scientific data:
  - "*We heard from experts* that this response was greater than that seen in placebo arms of most trials of topicals and may reflect that comparator preparations in some older trials included compounds that could be irritating and induce dermatitis"(page 36, emphasis added).
  - "*We have heard from experts* and patient groups that concerns about the safety of the other topical agents may be greater than is warranted…" (page 36, emphasis added)
    - In both cases above, ICER makes general statements attributed to "experts", but does not reveal the names or qualifications of these individuals, making it difficult to interpret the veracity of the claims made.

- Statements which misrepresent crisaborole's potential use or value:
  - "Trials of crisaborole…*did not assess potentially important outcomes* including psychologic and quality of life outcomes…" (page 37, emphasis added).
    - Note that crisaborole clinical trials did include quality of life outcomes, but these data were not included in the pivotal study publications. These data have been presented.[5]

[3] Lewis-Jones S. Quality of life and childhood atopic dermatitis: the misery of living with childhood eczema. Int J Clin Pract 2006; 60(8): 984–992
[4] Holm EA et al. Life Quality Assessment Among Patients With Atopic Eczema. The British Journal of Dermatology. 2006;154(4):819-825.
[5] Hebert AA, et al. Crisaborole Topical Ointment, 2%, Demonstrates Improvement in the Quality of Life of Patients With Mild to Moderate Atopic DermatitisFall Clinical Dermatology Conference. 2015 ;Oct 1-4; Las Vegas, NV.

We ask that ICER carefully review the entirety of its report to identify and remove these and any other potentially misleading statements made regarding the scientific data regarding crisaborole.

Concern #3: ICER should clarify the differences between vehicles and placebo in AD treatment, and consider the impact of changes in vehicles over time

Throughout its report, ICER refers to the vehicles used in treatment of AD as placebo. It is important to note that scientific consensus has delinieated a clear and important role for vehicles in the treatment of dermatologic conditions like AD, namely that vehicles should (a) efficiently deliver and release the drug to the skin, (b) sustain drug substance level in target tissue to provide pharmacological effect, and (c) be acceptable to the patient.[6]

Experts have also noted that:

- the chemical and physical characteristics of individual ingredients determine performance of a product's formulation[7];
- properties of vehicle formulations may influence drug delivery, efficacy, and tolerance profiles of topical medications[7,8,9];
- excipients have more pronounced effects in the skin than previously considered and can improve clinical appearance and skin barrier function;
- petrolatum has an immediate barrier-repairing effect in delipidized stratum corneum[7]

As such, we recommend that ICER clarify the role of vehicle in the treatment of AD, and consider how changes in vehicle over time may have impacted the results of clinical trials for AD treatments.

Concern #4: ICER should clarify its process for how patient input was gathered and considered as part of its report.

In recent months, ICER has stated its intent to increase its level of patient engagement as part of its reviews. On page 9 of the draft report, ICER references "discussions with patient groups and clinicians", and on pages 13 and 14 offers a brief summary of the insights gained from conversations with patients.

While we appreciate ICER's efforts to improve its patient engagement, we note a clear lack of transparency around the process for how inputs on patient perspectives were gathered and ultimately, how these inputs impacted (or did not impact) the findings. Greater clarity is needed to help resolve a number of questions that we (and likely other) stakeholders have, including:

- How many and which specific organization(s) did ICER engage? Is ICER confident that it has the full perspective of the entire AD patient community, which spans many different types of patient subgroups (e.g., based on age, disease severity, expected outcomes of treatment etc)?

- Did ICER speak to patients in addition to advocates (who, while knowledgeable, may not be AD patients themselves, and therefore may have a different set of perspectives)?

- How knowledgeable were these organization(s) with respect to the intent and processes of value assessment? Did they understand what the objectives of the review were, and did they understand the underlying methodologies to be implemented? What were their expectations for how their inputs will be utilized? Were these expectations met?

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[6] Vertuani S et al. The Topical Vehicle as a Key Factor in the Management of the Psoriatic Patients' Therapy. G Ital Dermatol Venereol. 2013;148(6):679-685

[7] Loden M. Role of topical emollients and moisturizers in the treatment of dry skin barrier disorders Am J Cliln Dermatol. 2003;4(11):771-788

[8] Thomsen SF. Atopic Dermatitis: Natural History, Diagnosis, and Treatment . ISRN Allergy. 2014; http://dx.doi.org/10.1155/2014/354250

[9] Sajic D et al. A Look at Epidermal Barrier Function in Atopic Dermatitis: Physiologic Lipid Replacement and the Role of Ceramides. Skin Therapy Letter 2015. http://www.skintherapyletter.com/2012/17.7/2.html

- What kinds of questions were posed by ICER to the patient advocacy groups? Did ICER send surveys? Did ICER engage in open-ended dialogue?

- Were patient groups asked about patient experiences across the spectrum of disease severity? If so, how did this influence ICER's approach?

- Were patient groups asked about what outcomes matter most to patients – and if so, was that information being considered as part of the ICER review?

We believe that these types of questions are critically important to answer, as they will allow ICER and its stakeholders to have an informed discussion in full context about how patient engagement is currently being incorporated into ICERs value assessment analyses, and how that process could be improved.

Concluding remarks

In this letter, we have sought to highlight a number of key limitations and concerns that we believe may critically impact the results reported in the draft AD report, and the interpretation of ICER's findings. We respectfully ask that ICER acknowledge our feedback and make the necessary efforts to address these issues, so that patients, physicians, and other stakeholders can have an unbiased perspective from which to consider the value of newer treatments for AD.

Kind regards,

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Pfizer, Inc.

Sanofi Genzyme and Regeneron Pharmaceuticals welcome the opportunity to provide feedback on the Institute for Clinical and Economic Review's (ICER) Draft Evidence Report on the comparative clinical effectiveness and value of dupilumab for the treatment of patients with moderate-to-severe atopic dermatitis (AD).

First of all, we want to acknowledge the good work done by ICER on this report including the economic modelling. In general, we agree with most aspects of the report. However, there are a few points that we recommend ICER reconsider in the final report. Our comments are summarized below and are explained in more detail in the subsequent sections.

- ***Cost-effectiveness.*** We believe that the cost-effectiveness analysis should be presented for the full moderate-to-severe AD population only, without stratification by AD disease severity.
- ***Comparative clinical effectiveness.*** We suggest ICER emphasize that while there are no high quality randomized controlled trials (RCTs) evaluating the benefit/risk profile of cyclosporine in AD, there is a substantial amount of data from high quality RCTs evaluating the benefit/risk profile of dupilumab use. In these RCTs, dupilumab demonstrated a favorable benefit/risk profile in adult patients with moderate-to-severe AD whose disease was not adequately controlled with topical prescription therapies or when those therapies were not advisable.
- ***Potential budget impact***. We request that ICER provide more details on the budget impact analysis methodology.

Below we outline these issues and provide our recommendations in more detail.

The cost-effectiveness analysis should be presented for the full moderate-to-severe AD population only without stratification by AD disease severity.

Measuring disease severity in clinical trials based on Investigator's Global Assessment (IGA) at isolated time points (such as at study entry/baseline) is not necessarily indicative of what patients may experience during the course of their disease, since AD is a chronic disease where the severity of signs and symptoms wax and wane with a high degree of fluctuation.

In the clinical setting, disease severity is determined based on a subjective assessment by physicians, which integrates AD signs, the patient's symptoms and their duration, response to current treatment, and the impact of the disease on quality-of-life (QoL). As indicated in the Draft Evidence Report on page 6, "Disease severity is not consistently defined and frequently involves patient/parent self-report in epidemiologic studies, and global clinical assessments used in trials (such as the Investigator's Global Assessment [IGA]). However, even with global clinical assessment measures, there are many variations used in studies."

In fact, severity scales used in clinical trials, such as the IGA, do not necessarily correlate with the intensity of patient symptoms or degree of impact on QoL. Our clinical trial data suggest that there are no clinically meaningful differences in patient-assessed symptoms and QoL between patients with severe (IGA=4) and moderate (IGA=3) AD. For example, the minimal clinically

important differences (MCID) for the pruritus numeric rating scale (NRS), Patient Oriented Eczema Measure (POEM) and Dermatology Life Quality Index (DLQI) are 3, 4, and 4, respectively. The differences in the pruritus NRS, POEM and DLQI between patients with baseline IGA=4 and patients with baseline IGA=3, were 0.53, 3.1, and 2.5, respectively, which are all below the MCIDs for the respective measures [1].

To summarize the above points, a patient's need for dupilumab treatment is not defined by clear demarcation of moderate versus severe disease as measured by IGA, but relies on a dichotomized assessment of whether or not patients with moderate-to-severe AD warrant such therapy because their disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

Thus, the reported individual cost-effectiveness analyses of dupilumab based on baseline IGA scores of 4 versus 3 are of limited clinical utility. These may be interpreted to imply that stakeholders such as physicians should follow treatment plans solely based on the severity of skin signs without considering patients' symptoms and QoL.

Finally, ICER's assessment of the effectiveness and value for the treatment of other indications such as psoriasis did not include separate cost-effectiveness assessments of moderate versus severe psoriasis. A similar approach should be taken for ICER's assessment of dupilumab for the treatment of atopic dermatitis.

Recommendations:

1. Assess the value of dupilumab as per the clinical trial design for the integrated moderate-to-severe population whose disease is not adequately controlled with topical prescription therapies or for whom topical therapies are not advisable. In particular, results for cost-effectiveness on page 44 in the Draft Evidence Report should not be stratified by disease severity.
2. Combine the voting questions on long-term value and pose the question as follows:

> *"Given the available evidence on comparative clinical effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, in adults with* ***moderate-to-severe*** *atopic dermatitis who have failed topical therapy, what is the long-term value for money of dupilumab compared with no systemic treatment? (Low, Intermediate, High)"*

Adjustments should be made to the content related to the qualitative comparison of dupilumab and cyclosporine.

First, the Evidence Report should clearly note that cyclosporine is not approved in the US for the treatment of AD and is only sparsely used. Based on the cyclosporine product label for other indications, serious side effects are associated with its use including, but not limited to, risks for malignancies, serious infection, hypertension, renal structural damages, and nephrotoxicity. Due to these long-term safety issues, physicians hesitate to prescribe cyclosporine for use in AD patients.

Second, comparison of clinical utility between dupilumab and cyclosporine should be based on an integrated assessment of the benefit/risk profiles of these therapies rather than on separate and

general comparisons of efficacy and safety, respectively. In particular, the Draft Evidence Report concludes on page 29 that: (i) "Dupilumab appears likely to be at least as effective as cyclosporine…", and (ii) "… short-term experience with dupilumab suggests it may be safer than cyclosporine."

The above statements in ICER's Draft Evidence Report fail to clearly describe the distinctly more favorable benefit/risk profile of dupilumab compared with cyclosporine in the management of this chronic disease.

Additionally, the statement in the Draft Evidence Report on page 31 "Cyclosporine has important toxicities, and is generally not used for more than one year," is based on empirical clinical experience due to the lack of high quality RCTs evaluating its benefit/risk profile. However, demonstrating a therapy's favorable benefit/risk profile over a long study period (e.g., 1 year) is highly meaningful in the context of a chronic disease such as AD.

In contrast with cyclosporine, there is a substantial amount of data from high quality RCTs evaluating the benefit/risk profile of dupilumab [2]. These RCTs, in which more than 2,000 patients were exposed to dupilumab, demonstrated that dupilumab has a favorable benefit/risk profile in adult patients with moderate-to-severe AD whose disease was not adequately controlled with topical prescription therapies or when those therapies were not advisable.

Failure to highlight the favorable benefit/risk profile of dupilumab based on high quality clinical trial data relative to the lack of quality data for cyclosporine, undermines the potential long-term value of dupilumab to patients who are eligible for treatment with this drug.

Recommendations:

3. Modify characterization of comparative clinical effectiveness of dupilumab and cyclosporine to reflect the discussion above.
4. Remove Voting Question 3 in the Draft Voting Questions document as it is not feasible to perform an evidence-based assessment of the long-term value of cyclosporine compared with non-systemic treatment or dupilumab.

More details should be provided on the methodology of the budget impact analysis

More details should be included in the report to facilitate replication of the budget impact analysis by stakeholders. In particular, additional explanation for the calculations leading to the results presented in Table 21 on page 50 of the Draft Evidence Report would be valuable. Also, clarifying if the uptake results are annual or cumulative over 5 years would be helpful.

Finally, the titles/description of the tables noted in the text on pages 48-50 do not match the titles of the respective table numbers.

Conclusion

We appreciate ICER's consideration of our comments and recommendations.

Sincerely,

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