For Atopic Dermatitis

Do these new drugs meet an important need?

What is atopic dermatitis?

Atopic dermatitis is a chronic skin condition characterized by itchy and dry skin. Atopic dermatitis is a subtype of eczema, though the terms are often used interchangeably.

In the United States, atopic dermatitis affects about **11% of children** and **3%-7% of adults**. Although most patients have mild disease, approximately 4%-7% of children with atopic dermatitis have severe disease, and the percentage is likely higher in adults.

Atopic dermatitis can have **significant impacts on quality of life**, particularly with more severe disease, but also in some patients with mild or moderate disease. Itching, in particular, can disrupt sleep, which leads to drowsiness, irritability, psychological stress, and impaired performance in school and at work. In addition, the physical effects of atopic dermatitis on the skin can lead to social stress and isolation.

Treating atopic dermatitis

Atopic dermatitis is often managed by vigilant care of the skin, including regular use of emollients (moisturizers) along with periodic use of a topical corticosteroid or long-term use of a topical calcineurin inhibitor. Patients whose disease cannot be controlled with topical therapy can be treated with phototherapy or medications such as cyclosporine or azathioprine, but those medications have important side effects and are not widely used.

Drugs under review

Two recently approved therapies offer additional options for patients with atopic dermatitis:

- **Crisaborole (Eucrisa™, Pfizer, Inc.)** is a topical medication for use in adults and children with mild-to-moderate atopic dermatitis. It is a potential alternative to topical corticosteroids or calcineurin inhibitors.
- **Dupilumab (Dupixent®, Sanofi-Regeneron)** is an injectable medication for moderate-to-severe atopic dermatitis in adults. Dupilumab was approved in March of 2017 and is expected to provide an important therapeutic option for many patients who have not previously had an adequate response to treatment.

How strong is the evidence that **dupilumab** improves outcomes for patients with moderate-to-severe atopic dermatitis?

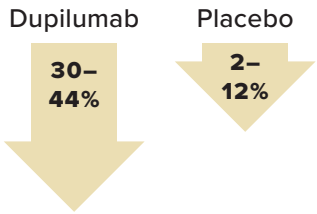
Clinical Outcomes

Compared to placebo:

Investigator's Global Assessment (IGA)

A clinician-reported outcome measure to determine severity of atopic dermatitis.

30-44% of patients treated with dupilumab had decreases in severity, compared to 2-12% for placebo.



Eczema Area Severity Index (EASI)

The EASI assesses the severity of and body surface area affected by symptoms of atopic dermatitis. EASI outcomes are measured as a percentage improvement in EASI score from baseline.

Compared with placebo, dupilumab substantially increased the likelihood of achieving a 50%, 75%, or 90% improvement of the EASI score from baseline.

Compared to other treatments:

Dupilumab appears likely to be **at least as effective as cyclosporine and more effective than phototherapy** at controlling atopic dermatitis. Short-term evidence on dupilumab suggests it may be safer than cyclosporine.

Patient-Reported Outcomes

- **Quality of Life:** Dupilumab improved patient quality of life as measured by the Dermatology Life Quality Index (DLQI).
- **Symptom Control:** Dupilumab improved measures of pruritus and improved scores on measures looking at broader patient outcomes, patient-reported outcomes, and anxiety and depression.

Harms

Severe or serious adverse events were rare during trials. Injection site reaction, cold symptoms, and headache were the most common side effects.

Dupilumab may also be associated with an increased risk for conjunctivitis.

How strong is the evidence that dupilumab improves outcomes for patients with moderate-to-severe atopic dermatitis? (continued)

Sources of Uncertainty

- **Limited long-term data:** Because of dupilumab's novel mechanism of action, toxicities and adverse events that haven't been observed yet may surface over time. There is also limited evidence on the expected duration of response to dupilumab.
- **Lack of head-to-head trials:** There are no head-to-head trials comparing dupilumab with other systemic therapies, so it is more challenging to assess the comparative benefits and harms.
- **Relative safety:** Limited experience with dupilumab makes it difficult to be certain of the relative safety of dupilumab versus established immunotherapies.
- **Generalizability:** The severity of disease was high in the clinical trials; it is uncertain whether patients receiving prescriptions for dupilumab in clinical practice will have similar levels of severity.

ICER Evidence Rating

- 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** relative to treatment with moisturizers 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.

How strong is the evidence that **crisaborole** improves outcomes for patients with mild-to-moderate atopic dermatitis?

Clinical Outcomes

Compared to placebo:

- **Investigator's Static Global Assessment (ISGA):** Crisaborole, compared with a placebo ointment that does not contain active drug, modestly increased the likelihood of meeting targets representing successful outcomes.
- **Other:** Crisaborole showed statistically significantly higher rates of improvement in erythema, exudation, excoriation, induration/papulation, and lichenification than placebo ointment.

No identified studies compared crisaborole to other active treatments.

Patient-Reported Outcomes

- **Pruritus:** Crisaborole modestly reduced itching.
- **Quality of Life:** Data also showed modest improvements on measures of quality of life and caregiver burden in patients treated with crisaborole; however, it was unclear if the improvements would be considered clinically meaningful.

Harms

Severe or serious adverse events were rare in all three clinical trials of crisaborole

The most common adverse events (AEs) with crisaborole at four weeks were pain or itching at the application site and fever.

Sources of Uncertainty

- **No head-to-head data:** There are no head-to-head trials comparing crisaborole with the other topical agents that would typically be used in patients with mild-to-moderate atopic dermatitis.
- **Relative Efficacy:** There is substantial uncertainty as to the relative efficacy of crisaborole. It is uncertain from the available evidence whether the patients who received crisaborole in clinical trials had had an inadequate response to existing pharmacologic and nonpharmacologic therapies for atopic dermatitis.
- **Long-term Safety:** While crisaborole was well tolerated over short periods of time (28 days in most trials), it is difficult to assess its safety compared with the other topical agents.

ICER Evidence Rating

For patients with mild-to-moderate atopic dermatitis, **we have inadequate evidence on both the relative efficacy and the relative safety of crisaborole**, although the efficacy of crisaborole appears likely to be less than that of topical tacrolimus and higher potency topical corticosteroids.

What is a fair price for **dupilumab** based on its value to patients and the health care system?

Given data availability challenges and anticipated clinical uptake, we did not include crisaborole in our economic evaluation.

Long-Term Cost-Effectiveness at Net Price

$101,800 per QALY *Compared to usual care*

For patients with severe atopic dermatitis: $78,300 per QALY
For patients with moderate atopic dermatitis: $130,800 per QALY

The manufacturer informed ICER that the average net price of dupilumab in the United States will not exceed $31,000. Using that price, we estimated the cost-effectiveness of dupilumab versus usual care over a lifetime time horizon for adult patients with moderate-to-severe atopic dermatitis. The incremental cost-effectiveness ratio was measured by calculating the cost per additional quality-adjusted life year (QALY). The cost per QALY range that is generally accepted as "reasonable" value in the United States is $50,000-$150,000.

ICER's Value-Based Price Benchmarks

Annual WAC*	Value-based price benchmarks	Change from WAC to reach benchmark*	Average net price within benchmark range?
$37,000	$30,516 -$43,726	18% discount to 18% increase	✓

Dupilumab's expected net price of $31,000 is well-aligned with the added benefit it provides to patients. **Dupilumab represents a good value for money.**

ICER's value-based price benchmark is a range associated with the prices needed to achieve long-term cost-effectiveness between $100,000–$150,000 per QALY.

*Wholesale Acquisition Cost

What is a fair price for **dupilumab** based on its value to patients and the health care system? (continued)

Potential Short-Term Budget Impact at List Price

Results from our potential budget impact analysis suggest that the average potential budgetary impact over five years at the discounted price of $31,000 for dupilumab was an additional per-patient cost of approximately $18,400. Our analysis estimated that approximately 5% of eligible patients could be treated in a given year without crossing the ICER budget impact threshold of $915 million at the discounted WAC.

The relatively low proportion of patients who could be treated is due in part to dupilumab being a new treatment in an area with few current options. Because it is not displacing current drug treatments, there are fewer offsetting costs.

Access and Affordability Alert

- Although the price for dupilumab is aligned with value, ICER notes that there is an access and affordability alert. Estimates from clinical experts and the manufacturer suggest that the number of patients whom clinicians may desire to treat will result in short-term costs that can create strains on health care budgets.
- Policymakers, payers, clinical experts, patient groups, and the manufacturer should continue to explore ways to manage affordability and maintain access to this treatment in a sustainable manner. As part of this effort, all stakeholders should seek collaborative ways to reduce ineffective and low-value care so that patients can benefit from this important new therapy.

Public Deliberation and Evidence Votes

Midwest Comparative Effectiveness Public Advisory Council Votes

The Midwest Comparative Effectiveness Public Advisory Council deliberated on key questions raised by ICER's report at a public meeting on May 25, 2017. The results of the votes are presented below. More detail on the voting results is provided in the full report.

1. In patients with mild-to-moderate atopic dermatitis, is the evidence adequate to demonstrate that the net health benefit of treatment with crisaborole is greater than that of treatment with topical corticosteroids or topical calcineurin inhibitors?

Yes: 2 votes	No: 9 votes

2. In adults with moderate-to-severe atopic dermatitis who have failed topical therapy, is the evidence adequate to demonstrate that treatment with dupilumab provides additional net health benefits beyond continued non-pharmacologic treatments such as emollients?

Yes: 11 votes	No: 0 votes

3. In adults with moderate-to-severe atopic dermatitis who have failed topical therapy, is the evidence adequate to demonstrate that the net health benefit of treatment with dupilumab is greater than that of treatment with cyclosporine?

Yes: 10 votes	No: 1 vote

4. Given the available evidence on comparative clinical effectiveness and incremental cost effectiveness, and considering other benefits, disadvantages, and contextual considerations, in a mixed population of 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: 0 votes	Intermediate: 8 votes	High: 3 votes

5. Given the available evidence on comparative clinical effectiveness and incremental cost effectiveness, and considering other benefits, disadvantages, and contextual considerations, in adults with moderate atopic dermatitis who have failed topical therapy, what is the long-term value for money of dupilumab compared with no systemic treatment?

Low: 0 votes	Intermediate: 9 votes	High: 2 votes

6. Given the available evidence on comparative clinical effectiveness and incremental cost effectiveness, and considering other benefits, disadvantages, and contextual considerations, in adults with severe atopic dermatitis who have failed topical therapy, what is the long-term value for money of dupilumab compared with no systemic treatment?

Low: 0 votes	Intermediate: 0 votes	High: 11 votes

Key Policy Implications and Recommendations

The Midwest CEPAC engaged in a moderated discussion with a policy roundtable of subject-matter experts about how best to apply evidence on treatments for atopic dermatitis in policy and practice. The roundtable included patients, clinical experts, a drug manufacturer representative, and a private payer representative.

The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. Below are the top-line policy implications; for more information please see the full report.

For Payers and Pharmacy Benefits Managers

While ICER's analyses found the price of dupilumab to be in line with its benefit, the broad range of severity of atopic dermatitis, limited long-term data on dupilumab's efficacy and appropriate use, and issues with affordability will lead payers to design evidence-based pre-authorization coverage criteria.

Criteria are likely to take the following into account:

- **Specialist prescribing:** Payers may consider requiring specialist prescribing of dupilumab.
- **Severity measures:** There is no consensus on how to define severity. Payers using severity level as part of coverage policy should consider accepting the maximum severity of disease across multiple measures.
- **Trials of therapy:** Payers may consider inadequate response to one month of topical treatment with a moderate potency corticosteroid or tacrolimus 0.1% as an appropriate trial of treatment prior to coverage of dupilumab. Due to safety concerns with existing systemic therapies, clinical experts suggested that patients should not be required to try other systemic treatments such as cyclosporine before being covered for dupilumab.
- **Stopping rules:** Payers may require some measure of success for continuation of coverage past a certain number of months. Clinical experts noted EASI 50 as a potentially appropriate measure for some patients, but emphasized that the patient and provider should be involved in assessing the level of response. Experts also noted that after prolonged successful treatment, dupilumab should not be stopped abruptly, but trials of tapering may be appropriate.
- **Use in children:** Trials to evaluate dupilumab in children are ongoing. In the interim, health plans should ensure that clinicians assessing coverage exceptions for children are expert in this drug's risks and benefits and in the spectrum of atopic dermatitis.

For Researchers, Clinicians, Manufacturers, and Patient Groups

- Work to develop a standard definition of disease severity and standard outcome measures. Patient groups should have a leading role in these efforts, and promote use of these definitions and measures in clinical trials.

For Specialty Societies

- Educate members in the appropriate use of new medications for atopic dermatitis.

Key Policy Implications and Recommendations (continued)

For Clinicians and Patient Groups

- Communicate potential risks of new treatments, including uncertainty around the long-term benefit and potential harms of any new therapy.

For Manufacturers and Researchers

- Perform direct comparisons of therapies when appropriate to better inform decision-making.

Conclusion

Comparative Clinical Effectiveness

Treatment with dupilumab resulted in substantial improvements in atopic dermatitis in the majority of patients who were studied. In addition to improving the severity of atopic dermatitis and reducing pruritus, treatment improved quality of life and the effects of atopic dermatitis on sleep, anxiety, and depression. Our review found inadequate evidence to assess the relative efficacy of crisaborole compared with the other topical therapies for atopic dermatitis.

Comparative Value

Our economic modeling analysis indicates that dupilumab improves health outcomes compared to usual care, but with additional costs. At the discounted price of dupilumab used in ICER's report, the incremental cost-effectiveness ratio was at or below commonly cited thresholds for cost-effectiveness, making dupilumab a good value for money in the long-term.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent nonprofit research institute that produces reports analyzing the evidence on the effectiveness and value of drugs and other medical services. ICER's reports include evidence-based calculations of prices for new drugs that accurately reflect the degree of improvement expected in long-term patient outcomes, while also highlighting price levels that might contribute to unaffordable short-term cost growth for the overall health care system.

ICER's reports incorporate extensive input from all stakeholders and are the subject of public hearings through three core programs: the California Technology Assessment Forum (CTAF), the Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) and the New England Comparative Effectiveness Public Advisory Council (New England CEPAC). These independent panels review ICER's reports at public meetings to deliberate on the evidence and develop recommendations for how patients, clinicians, insurers, and policymakers can improve the quality and value of health care. For more information about ICER, please visit ICER's website (www.icer-review.org).

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