Summary

KEY FINDINGS

Intervention	Evidence Rating	Annual WAC	Annual Health-Benefit Price Benchmark	Change from Annual Price Required to Reach Threshold Price
Abrocitinib*	P/I (promising but inconclusive), when compared to topical therapies	N/A	$30,600-$41,800	N/A
Baricitinib*	P/I (promising but inconclusive), when compared to topical therapies C- (moderate certainty that intervention is comparable or inferior to dupilumab)	$29,000	$24,400-$33,300	0%-16%
Tralokinumab*	P/I (promising but inconclusive), when compared to topical therapies C- (moderate certainty that intervention is comparable or inferior to dupilumab)	N/A	$25,700-$35,000	N/A
Upadacitinib*	P/I (promising but inconclusive), when compared to topical therapies	$64,300	$30,400-$41,500	35%-53%
Dupilumab	Comparator	$41,800	$29,000-$39,500	6%-31%

* The evidence is also insufficient ("I") to compare abrocitinib, tralokinumab, baricitinib, and upadacitinib to each other.

WAC: wholesale acquisition cost; evLYG: equal value life year gained; QALY: quality-adjusted life year;

N/A: Not applicable (NA) as placeholder prices were used

"Both in this review and in our 2017 review, we heard from multiple stakeholders how disruptive severe atopic dermatitis can be for patients and their families, affecting work, school, sleep, mental health, and self-assurance. For many people, atopic dermatitis is a relatively mild condition, but atopic dermatitis can be a severe, chronic disease with significant effects on quality of life. Dupilumab was a major advance, but it does not work for all patients, and new therapies are needed. If they prove safe, JAK inhibitors are likely to benefit many patients, including some who did not get adequate relief with dupilumab.At our public meeting, the New England CEPAC discussed the importance of ensuring these new therapies for atopic dermatitis improve the health of patients and families and do not aggravate existing health inequities. Clinical experts and patients highlighted that the high cost of new therapies might worsen disparities in accessing care."

– ICER Chief Medical Officer David Rind,

Summary

THEMES AND RECOMMENDATIONS

- All stakeholders have a responsibility and an important role to play in ensuring that effective new treatment options for patients with atopic dermatitis are introduced in a way that will help reduce health inequities.
- Payers should only use step therapy when it provides adequate flexibility to meet the needs of diverse patients and when implementation can meet established standards of transparency and efficiency.
- Specialty societies should update treatment guidelines for patients with atopic dermatitis to reflect current treatment options in a form that is easy to interpret and use by clinicians, patients and payers.
- Manufacturers, payers and patient advocacy groups should support pricing and rebate reform efforts that will create better rewards for clinical and economic value while also helping patients afford access to the treatments they need.

Clinical Analyses

KEY CLINICAL BENEFITS STUDIED IN CLINICAL TRIALS

Atopic dermatitis is a common, chronic skin condition with persistent or relapsing lesions that are itchy, inflamed, and dry. Commonly referred to as "eczema," atopic dermatitis affects both children and adults. Symptoms of itching and even skin pain vary in severity, but can affect sleep, cause psychological distress, and result in difficulty with performance at school or work. The appearance of the skin can also lead to social embarrassment and isolation. The net effect is that atopic dermatitis can have a profound effect on all aspects of patients' lives and those of their family and caregivers. In the United States (US), atopic dermatitis is estimated to affect around 11-15% of children and 7-10% of adults. The overall costs associated with atopic dermatitis are estimated to be $5.3 billion dollars in the US, including over $1 billion in health care costs. Atopic dermatitis also can lead to work and productivity loss.

Patients and caregivers emphasized the importance of having measures of treatment outcomes that are most meaningful to them. Itching and pain were seen as the key outcomes, but their impact on sleep, increased distraction, worry, anxiety and other aspects of life varied according to an individual's particular circumstances. For example, some patients reflected that when they were adolescents, appearance was most important to them. As they got older, other issues such as the impact on the skin in terms of pain and infections became more important. Though all recognized atopic dermatitis as a chronic condition, the importance of flares and the need to break cycles of worsening disease was also emphasized. Since many individuals also are impacted by other conditions such as asthma and allergies, and some treatments improve these conditions as well, we heard about the importance of thinking broadly about the benefits of treatments. Since itching is the most bothersome symptom for most patients, the importance of measuring the impact of treatments on itch and associated issues such as sleep disruption are needed. The importance of comprehensive outcome measures that capture the diversity and impact of atopic dermatitis over time was emphasized.

Clinical Analyses

ICER reviewed dupilumab for moderate-to-severe atopic dermatitis and topical crisaborole for mild-to-moderate atopic dermatitis in 2017. A number of new biologic therapies are available or being evaluated in patients with atopic dermatitis. Tralokinumab, a monoclonal antibody that blocks IL-13 receptor binding is given subcutaneously and is under investigation for patients with moderate-to-severe atopic dermatitis. Abrocitinib, baricitinib, and upadacitinib are oral Janus kinase (JAK) inhibitors that are also being evaluated for patients with moderate-to-severe atopic dermatitis. Concerns about the safety of oral JAK inhibitors that are approved for other conditions has led the U.S. Food and Drug Administration (FDA) to extend the review period for these drugs, and tralokinumab received a Complete Response Letter from the FDA requesting additional data relating to a device component used to inject tralokinumab. A topical JAK inhibitor, ruxolitinib cream, is being evaluated for patients with mild-to-moderate atopic dermatitis, and its review period has also been extended by the FDA.

In the moderate-to-severe population, the four interventions all improved skin findings compared with placebo, and, where assessed, appeared to improve itch, sleep, and quality of life. Quantitative indirect comparisons across the new agents and dupilumab, as well as head-to-head comparisons between two of the agents (upadacitinib and abrocitinib) and dupilumab suggest that higher doses of updadacitinib and possibly abrocitinib are somewhat more effective than dupilumab, while baricitinib (at the doses likely to be approved) and tralokinumab are likely somewhat less effective than dupilumab; however, there is substantial uncertainty in these comparisons. Resolution of itch may occur more quickly with higher-dose abrocitinib than with dupilumab.

Safety is an important consideration with biologic therapies and, as above there have been particular concerns about the safety of oral JAK inhibitors when used for other conditions. Concerns about lack of long-term data for dupilumab, noted in ICER's 2017 report, have been alleviated over time based on published data and widespread use in clinical practice. Tralokinumab is a novel inhibitor of IL-13 that works through a mechanism more similar to dupilumab than the JAK inhibitors, but lacks the same long-term safety profile of dupilumab.

An additional consideration in comparing therapies is that many patients with atopic dermatitis have comorbid atopic conditions such as asthma, and dupilumab has proven efficacy in treating certain patients with asthma or chronic rhinosinusitis.

Taking into consideration the above information on short-term benefits seen in the trials but limited data and concerns about long-term safety, especially for oral JAK inhibitors, we concluded the evidence on net health benefit for abrocitinib, baricitinib, upadacitinib, and tralokinumab compared with topical therapies alone was promising but inconclusive ("P/I") and compared to each other was insufficient ("I"). We concluded that the evidence for net health benefit for abrocitinib and upadacitinib compared with dupilumab was also insufficient ("I"), and that the net health benefit of baricitinib and tralokinumab were comparable or inferior ("C-") when compared with dupilumab.

Since the baricitinib and tralokinumab trials only included adults and abrocitinib and upadacitinib trials enrolled small numbers of patients younger than age 18, there is greater uncertainty for adolescents with the new therapies.

In the mild-to-moderate population, topical ruxolitinib cream was more effective than vehicle (placebo). While ruxolitinib cream also appeared to

Clinical Analyses

be more effective than a medium potency topical corticosteroid, it was not compared to more potent topical corticosteroids and differences in trial designs precluded quantitative indirect comparisons across topical therapies. There is currently limited information on long-term safety of ruxolitinib cream. As a topical JAK inhibitor therapy, safety concerns are likely not as great as with oral JAK inhibitors, but there still is systemic absorption of the topical agent. Topical corticosteroids have known harms both to the skin and, particularly with higher potency preparations in children, a risk for systemic harms. Topical calcineurin inhibitors carry a "black box" warning for a potential risk for causing malignancy, although many clinical experts feel the evidence does not warrant this concern.

We assess the net health benefit forruxolitinib cream compared with topical emollients to be comparable or better ("C++"). We consider the evidence for the net health benefit for ruxolitinib cream compared with other topical medications to be insufficient ("I").

Economic Analyses

LONG-TERM COST EFFECTIVENESS

We compared the cost and effectiveness of abrocitinib, baricitinib, tralokinumab and upadacitinib for moderate to severe atopic dermatitis to topical emollients (standard of care) and dupilumab, over a five-year time horizon taking a health system perspective.

Estimated net prices were used for baricitinib, upadacitinib and dupilumab that are currently marketed. For abrocitinib, we used the average of the net prices of baricitinib and upadacitinib as a placeholder. For tralokinumab, we used the net price of dupilumab as a placeholder.

Table 1 presents the incremental results from the base case cost-effectiveness analysis. Given no modeled gains in life years across the evaluated therapies, the cost per life year gained is not reported.

From the cost-effectiveness base case assuming the standard of care comparator, we estimated the Health Benefit Price Benchmarks (HBPBs) for each intervention. The HBPB range for abrocitinib is $30,600 to $41,800 (discounts not presented due to placeholder price); for baricitinib, $24,400 to $29,000 (16% discount to no discount from Wholesale Acquisition Cost (WAC) needed at the $150,000 threshold); for tralokinumab from $25,700 to $35,000 (discounts not presented due to placeholder price); for upadacitinib from $30,400 to $41,500 (discounts of 35% to 53% from WAC); and for dupilumab from $29,000 to $39,500 (discounts of 6% to 31% from WAC).

Economic Analyses

Table 1. Incremental Cost-Effectiveness Ratios for the Base Case

Intervention	Comparator	Cost per QALY Gained	Cost per evLYG
Abrocitinib*	SoC	$148,300	$148,300
Baricitinib	SoC	$71,600	$71,600
Tralokinumab*	SoC	$129,400	$129,400
Upadacitinib	SoC	$248,400	$248,400
Dupilumab	SoC	$110,300	$110,300
Abrocitinib*	Dupilumab	$303,400	$303,400
Baricitinib	Dupilumab	Less Costly, Less Effective	Less Costly, Less Effective
Tralokinumab*	Dupilumab	Less Costly, Less Effective	Less Costly, Less Effective
Upadacitinib	Dupilumab	$1,912,200	$1,912,200

evLYG: equal-value life-year gained, QALY: quality-adjusted life-year, SOC: Standard of Care

*Using a placeholder price

Note: The cost per QALY and cost per evLYG ratios were the same given that the treatments have not been shown to lengthen life.

VOTING RESULTS

For adults with moderate-to-severe atopic dermatitis, the New England CEPAC voted:

- 8-5 that the evidence was adequate to demonstrate that abrocitinib plus usual care provides a net health benefit when compared to usual care alone.
- 7-6 that the evidence was adequate to demonstrate that baricitinib added to usual care provides a net health benefit when compared to usual care alone.
- 9-4 that the evidence was adequate to demonstrate that upadacitinib added to usual care provides a net health benefit when compared to usual care alone.
- 11-2 that the evidence was adequate to demonstrate that tralokinumab added to usual care provides a net health benefit when compared to usual care alone.

For adolescents and adults with mild-to-moderate atopic dermatitis, the New England CEPAC voted:

- 12-1 that the evidence was adequate to demonstrate that ruxolitinib provides a net health benefit when compared to topical emollients alone.

Economic Analyses

POTENTIAL OTHER BENEFITS AND CONTEXTUAL CONSIDERATIONS

During their deliberations, panel members also weighed the therapies' other potential benefits, disadvantages, and contextual considerations. For both treatments, voting highlighted the following as particularly important for payers and other policymakers to note:

- The acuity of need for treatment based on the severity of atopic dermatitis;
- The magnitude of the lifetime impact on individual patients of atopic dermatitis;
- Patients' ability to achieve major life goals related to education, work, or family life;
- Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life.

POTENTIAL BUDGET IMPACT

For this analysis, we calculated the budget impact of new treatments (abrocitinib, baricitinib, tralokinumab, and upadacitinib) given these treatments' displacement of dupilumab plus usual care (assumed 10% mix) and usual care alone (90% mix) and by assigning 103,200 new individuals to each new treatment per year (for five years). Upon removing the placeholder prices and across all four treatments, the range of the percentage of those treated without crossing the potential budget impact annual threshold was between 8% and 79% for all prices evaluated.

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.org).