For moderate-to-severe plaque psoriasis

Do these new drugs meet an important need?

What Is Moderate-To-Severe Plaque Psoriasis?

Plaque psoriasis is a common disease that causes itchy, red, scaly, raised lesions on the skin, most often on the elbows, knees, scalp, and back. Moderate-to-severe plaque psoriasis is often defined as psoriasis affecting more than 5%-10% of the body. Chronic plaque psoriasis can significantly decrease quality of life, particularly if lesions are in areas that can affect daily functioning (e.g., the hands or soles of the feet) or social functioning (e.g., the face). There is no cure for plaque psoriasis, but it can be managed with topical therapies, phototherapy, and systemic therapies.

Chronic plaque psoriasis accounts for about 80% of all patients with psoriasis. Psoriasis affects about 3% of the population.

Treating Moderate-To-Severe Plaque Psoriasis

Standard treatment for psoriasis falls into four main categories:

- Topical therapies such as steroids, vitamin D analogs, retinoids, and calcineurin inhibitors
- Older systemic therapies, such as acetretin, cyclosporine, and methotrexate
- Phototherapy
- “Targeted immunomodulators,” including TNFα, IL-17A, IL 12/23, and PDE-4 agents

Roughly 70% to 80% of patients with plaque psoriasis have mild disease that can be adequately managed with topical therapy. Moderate-to-severe plaque psoriasis is generally treated with systemic therapies, phototherapy, and targeted immunomodulators—drugs that work by changing the body’s immune response.

Clinical interest in targeted immunomodulators is high, as many patients with moderate-to-severe plaque psoriasis do not see adequate or long-lasting benefit from topical therapies, older systemic therapies, or phototherapy. Our review focused on eight approved or expected to be approved targeted immunomodulators.

New Drugs Under Review

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Drug Name</th>
<th>Cost of Initiation*</th>
<th>Cost of Monthly Maintenance*</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNFα</td>
<td>Adalimumab (Humira®)</td>
<td>$14,361 (4 mo.)</td>
<td>$2,868</td>
</tr>
<tr>
<td></td>
<td>Etanercept (Enbrel®)</td>
<td>$17,283 (3 mo.)</td>
<td>$2,868</td>
</tr>
<tr>
<td></td>
<td>Infliximab (Remicade®)</td>
<td>$16,874 (10 wk.)</td>
<td>$1,948</td>
</tr>
<tr>
<td>IL 12/23</td>
<td>Ustekinumab (Stelara®)</td>
<td>$26,072 (3 mo.)</td>
<td>$3,256</td>
</tr>
<tr>
<td>IL-17A</td>
<td>Brodalumab (investigational)</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td></td>
<td>Ixekizumab (Taltz®)</td>
<td>$21,523 (3 mo.)</td>
<td>$2,681</td>
</tr>
<tr>
<td></td>
<td>Secukinumab (Cosentyx®)</td>
<td>$14,656 (3 mo.)</td>
<td>$2,439</td>
</tr>
<tr>
<td>PDE-4</td>
<td>Apremilast (Otezla®)</td>
<td>$7,549 (4 mo.)</td>
<td>$1,931</td>
</tr>
</tbody>
</table>

Most targeted immunomodulators are delivered by injection or infusion, with the exception of apremilast, an oral drug.

*Drug costs were obtained from SSR Health LLC, which combines information on net US dollar sales with unit sales to derive net pricing estimates per unit that include rebates and discounts across all payer types.

**Brodalumab is not yet FDA approved, and no price has been determined.
How strong is the evidence that these treatments improve patient outcomes?

**Psoriasis Area and Severity Index (PASI) Response**

The PASI measures the percent of body surface area with psoriatic lesions in each of four regions (head, trunk, arms, and legs) as well as the severity of the lesions in each region.

In clinical trials, the primary outcome sought was the proportion of patients achieving “PASI 75,” or a 75% improvement in score, during induction (between 10 to 16 weeks). There are few data comparing the effectiveness of targeted immunomodulators beyond the induction period.

- All drugs demonstrated substantially improved treatment response versus placebo.
- In direct comparison trials, ustekinumab, secukinumab, and ixekizumab were superior to etanercept. Secukinumab, brodalumab, and ixekizumab were superior to ustekinumab.
- In a network meta-analysis, a technique that combines direct and indirect evidence, ixekizumab had the highest likelihood of achieving PASI 75, followed by brodalumab, infliximab, secukinumab, ustekinumab, adalimumab, etanercept, and apremilast.

Results were similar on analyses that used different cutoffs for PASI improvement (i.e., PASI 50, 90, and 100), as well as on the Physicians’ Global Assessment, a physician-scored tool that measures psoriasis severity.

**Dermatology Life Quality Index (DLQI)**

The DLQI is a survey of ten questions relating to symptoms, feelings, daily activities, leisure, work, school, social interactions, clothing choice, sexual difficulties, and treatment problems.

The DLQI results generally mirrored those for the PASI 75. Infliximab produced the greatest relative benefit and apremilast produced the smallest relative benefit to placebo. In head-to-head trials, secukinumab and ixekizumab were superior to both etanercept and ustekinumab.

**Harms**

Severe or serious adverse events were rare during the induction phase of treatment.

- Infections (e.g., nasopharyngitis, upper respiratory tract infections, etc.), injection site or infusion reaction, headache, and nausea were the most common side effects with biologics. Infliximab appears to have higher rates of these events than other drugs.
- Apremilast, the only oral targeted immunomodulator, was associated with higher rates of diarrhea.

Longer-term safety data were variably reported so cross-drug comparisons were not possible.
How strong is the evidence that these treatments improve patient outcomes? (continued)

<table>
<thead>
<tr>
<th>Sources of Uncertainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Trials prohibited use of other medications (e.g., topical steroids) during the studies, which may not represent real-world practice in which next-best treatment would not be placebo. No studies have evaluated combination therapy.</td>
</tr>
<tr>
<td>• Longer-term data on both drug effectiveness and harms were variable.</td>
</tr>
<tr>
<td>• Assessments of real-world effectiveness are limited by lack of comparative data on non-standard dosing, whether increased (to preserve effectiveness) or decreased (to reduce costs).</td>
</tr>
<tr>
<td>• The PASI does not reflect potential differential impact of associated conditions, such as psoriatic arthritis, which are common among patients with psoriasis.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ICER’s Evidence Ratings</th>
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<tbody>
<tr>
<td>ICER’s analyses found that all drugs provide substantial net health benefits versus placebo. The report further concluded that, in general, IL-17A drugs (ixekizumab, secukinumab, brodalumab) provide incremental net health benefit over ustekinumab, apremilast, and etanercept, and at least comparable net health benefit to several other agents. ICER’s complete evidence ratings are available in the <a href="#">full report</a>.</td>
</tr>
</tbody>
</table>
What is a fair price for these new drugs based on their value to patients and the health care system?

### Long-Term Cost-Effectiveness at Net Price

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Cost/$QAL Y</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNFα</td>
<td>Adalimumab</td>
<td>$108,040/QAL Y</td>
</tr>
<tr>
<td></td>
<td>Etanercept</td>
<td>$117,769/QAL Y</td>
</tr>
<tr>
<td></td>
<td>Infliximab</td>
<td>$92,715/QAL Y</td>
</tr>
<tr>
<td>IL 12/23</td>
<td>Ustekinumab</td>
<td>$129,904/QAL Y</td>
</tr>
<tr>
<td>IL-17A</td>
<td>Brodalumab*</td>
<td>$94,030/QAL Y</td>
</tr>
<tr>
<td></td>
<td>Ixekizumab</td>
<td>$100,389/QAL Y</td>
</tr>
<tr>
<td></td>
<td>Secukinumab</td>
<td>$89,843/QAL Y</td>
</tr>
<tr>
<td>PDE-4</td>
<td>Apremilast</td>
<td>$89,610/QAL Y</td>
</tr>
</tbody>
</table>

ICER calculated the incremental cost-effectiveness ratio for each of the targeted therapies compared to non-targeted therapy.

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 US is $100,000-$150,000.

Drug costs were based on estimated net prices that account for discounts and rebates across payer types.

Based on assumed net prices, most drugs for moderate-to-severe plaque psoriasis were well within, if not below, the range for reasonable value, representing good long-term value for money.

*Results for brodalumab are tentative, as pricing is not available.

### Potential Short-term Budget Impact at Net Price

**Brodalumab:**

$239.8 million per year

**Ixekizumab:**

$266 million per year

Potential short-term budget impact at net price was evaluated only for the two newer agents, brodalumab and ixekizumab.

The proportion of psoriasis patients with plaque psoriasis has been estimated to be 79%, with about 18% having moderate-to-severe disease.

Applying these proportions to the projected 2016 U.S. population results in an estimate of approximately 36,750 incident cases of moderate-severe plaque psoriasis per year, or approximately 183,750 incident cases over five years, assuming equal incidence rates for each of the five years in our analysis. This was assumed to be the candidate population for treatment with these novel agents.

We assumed a 10% uptake for ixekizumab and a 10% uptake for brodalumab in the eligible population over five years.

Neither drug approached ICER’s annual threshold of $904 million, or the point at which the potential short-term budget impact could be so substantial that policymakers should consider whether special coverage, pricing, or payment mechanisms are needed to assure sustainable access to high-value care for all patients.
What is a fair price for these new drugs based on their value to patients and the health care system? (continued)

ICER’s Value-Based Price Benchmark

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Drug Name</th>
<th>Value-Based Price Benchmark per Pill/Vial</th>
<th>Change from Wholesale Acquisition Cost to Reach Benchmark</th>
<th>Average Net Price Within Benchmark Range?</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNFα</td>
<td>Adalimumab (40mg)</td>
<td>$1,311.40-$2,073.74</td>
<td>36% discount to 1% increase</td>
<td>✅</td>
</tr>
<tr>
<td></td>
<td>Etanercept (50mg)</td>
<td>$566.68-$989.98</td>
<td>3-45% discount</td>
<td>✅</td>
</tr>
<tr>
<td></td>
<td>Infliximab (100mg)</td>
<td>$857.54-$1,395.18</td>
<td>23% discount to 25% increase</td>
<td>✅</td>
</tr>
<tr>
<td>IL 12/23</td>
<td>Ustekinumab (45mg)</td>
<td>$5,886.50-$8,608.05</td>
<td>3-33% discount</td>
<td>✅</td>
</tr>
<tr>
<td>IL-17A</td>
<td>Ixekizumab (80mg)</td>
<td>$2,672.66-$3,795.25</td>
<td>15-40% discount</td>
<td>✅</td>
</tr>
<tr>
<td></td>
<td>Secukinumab (300mg)</td>
<td>$2,680.73 - $3,872</td>
<td>5-34% discount</td>
<td>✅</td>
</tr>
<tr>
<td>PDE-4</td>
<td>Apremilast (30mg)</td>
<td>$42.94-$83.64</td>
<td>0.4% discount to 94% increase</td>
<td>✅</td>
</tr>
</tbody>
</table>

As shown in the table, with the exception of adalimumab, apremilast, and infliximab, all drugs would require discounts from current WAC prices to fall within ICER’s threshold value range of $100,000 to $150,000/QALY. Importantly, however, our estimates of net prices bring all the drugs of interest either within this threshold value range or generate cost-effectiveness ratios that are already <$100,000 per QALY gained.

ICER’s value-based price benchmark is comprised of two components: a range associated with the prices needed to achieve long-term cost-effectiveness between $100,000–$150,000 per QALY; and the price at which the potential short-term budget impact could be so substantial that policymakers should consider whether special coverage, pricing, or payment mechanisms are needed to assure sustainable access to high-value care for all patients.
Public Deliberation and Evidence Votes

The New England Comparative Effectiveness Public Advisory Council deliberated on key questions raised by ICER’s report at a public meeting on November 18, 2016. The results of the votes are presented below. More detail on the voting results is provided in the full report.

Voting Summary

1. Is the evidence adequate to demonstrate that the net health benefit of apremilast is as good as that provided by any of the TNFα inhibitors?
   - Yes: 0 votes
   - No: 14 votes

2. Is the evidence adequate to distinguish the net health benefit among the IL-17A targeted drugs secukinumab, ixekizumab, and brodalumab?
   - Yes: 0 votes
   - No: 14 votes

2a. Is the evidence adequate to demonstrate that the net health benefit of IL-17A drugs as a class is better than that provided by adalimumab?
   - Yes: 5 votes
   - No: 9 votes

2b. Is the evidence adequate to demonstrate that the net health benefit of IL-17A drugs as a class is better than that provided by etanercept?
   - Yes: 14 votes
   - No: 0 votes

2c. Is the evidence adequate to demonstrate that the net health benefit of IL-17A drugs as a class is better than that provided by infliximab?
   - Yes: 1 votes
   - No: 13 votes
### New England Comparative Effectiveness Public Advisory Council Votes

3. Is the evidence adequate to demonstrate that the net health benefit of ustekinumab is better than that provided by adalimumab?

| Yes: 1 votes | No: 13 votes |

4. Is the evidence adequate to demonstrate that the net health benefit of ustekinumab is better than that provided by etanercept?

| Yes: 14 votes | No: 0 votes |

5. Is the evidence adequate to demonstrate that the net health benefit of ustekinumab is better than that provided by infliximab?

| Yes: 0 votes | No: 14 votes |
### Public Deliberation and Evidence Votes (continued)

#### New England Comparative Effectiveness Public Advisory Council Votes

#### Care Value Voting Results

6. Given the available evidence on comparative effectiveness and incremental cost-effectiveness using estimated discounted prices for private insurers presented in the report, and taking into account other benefits, disadvantages, and contextual considerations, what is the long-term value for money of the following drugs compared to continued non-targeted therapy?

**Adalimumab:**
- Low: 0 votes
- Intermediate: 11 votes
- High: 3 votes

**Etanercept:**
- Low: 2 votes
- Intermediate: 11 votes
- High: 1 votes

**Infliximab:**
- Low: 3 votes
- Intermediate: 8 votes
- High: 2 votes

**Ustekinumab:**
- Low: 3 votes
- Intermediate: 8 votes
- High: 2 votes

**Secukinumab:**
- Low: 0 votes
- Intermediate: 3 votes
- High: 11 votes

**Ixekizumab:**
- Low: 0 votes
- Intermediate: 6 votes
- High: 8 votes

**Brodalumab:**
*No comparative value vote was taken on brodalumab, as its anticipated approval by the FDA was delayed beyond the timeline of this review and thus no list price was available for consideration.*

**Apremilast:**
- Low: 0 votes
- Intermediate: 7 votes
- High: 7 votes

7. Given the available evidence on comparative clinical effectiveness and incremental cost-effectiveness, and taking into account other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment with ixekizumab and secukinumab versus etanercept?

- Low: 0 votes
- Intermediate: 1 votes
- High: 13 votes
Key Policy Implications and Recommendations

The New England CEPAC engaged in a moderated discussion about how best to apply evidence on targeted immunomodulators for plaque psoriasis in policy and practice. The roundtable included two clinical experts, two patient representatives, and two payer representatives. 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.

Specialty Societies and Patient Advocacy Groups

- Update outdated treatment guidelines for patients with moderate-to-severe chronic plaque psoriasis to provide better precision on the therapies that are appropriate for specific patient subpopulations. In addition, updated guidelines should be produced in a form that is easy to understand and easy-to-use by payers, clinicians, and patients.

Purchasers and Insurers

- Consider limiting or abolishing "step therapy" approaches to coverage.
  - Step-therapy can be appropriate for treating certain conditions, but given that all of the targeted immunomodulators have good value relative to non-targeted treatment, payers should strongly consider eliminating most step therapy requirements for patients with moderate-to-severe psoriasis. Any step therapy requiring initial use of TNFα inhibitors before other drugs should be reconsidered to allow rapid and permanent exceptions for patients with co-conditions, co-morbidities, or specific life requirements that make other drugs the best first choice among all available targeted immunomodulators.
  - If step therapy will be used:
    - Allow individuals switching insurers to bypass step therapy if they are already on an effective treatment.
    - Remove requirements for patients to have higher out-of-pocket expenses for “later step” treatments.
    - As alternative mechanisms to manage costs, consider developing indication-specific formulary designs and outcome-based payment contracts.
    - Co-payment and/or co-insurance for therapies should be based on prices net of discounts and rebates instead of list price.

Manufacturers

- Foster transparency in the rationale for price increases.
- Release treatment-specific quality-of-life data.

Researchers and Manufacturers

- Conduct research that directly compares real-world treatment options and sequential treatment effectiveness for both naïve and treatment-experienced patients.
- Generate additional information on the treatment durability of IL-17A agents.

Patient Advocacy Groups, Clinicians, and Researchers

- Patients and patient organizations should take a leadership role in the design of clinical trials and all stakeholders should advocate for rigorous study in diverse populations evaluating real-world comparative treatments.
- Lead research efforts to evaluate heritability of psoriasis and the impact of managing plaque psoriasis on caregivers and families.
Conclusion

**Clinical Effectiveness**

- Placebo-controlled trials indicated substantial improvements in clinical measures for all agents relative to placebo.

- Serious harms were rarely observed during the short duration of clinical trials; longer-term safety data were collected variably, making comparisons between agents problematic.

- In direct and indirect comparisons between agents, ixekizumab, secukinumab, and brodalumab appeared to provide a greater level of net health benefit than etanercept, ustekinumab, or apremilast and at least comparable net health benefit to several other agents.

**Comparative Value**

- While all targeted therapies reflected reasonably good value for money, it was seen that drugs with high first-line efficacy and low discontinuation rates provided greatest patient benefit.

- The newer IL-17A targeted therapies (brodalumab, ixekizumab, secukinumab) provided good monetary value in comparison to etanercept.

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**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](http://www.icer-review.org).