

## Background

### PLAQUE PSORIASIS

Plaque psoriasis is a common disease affecting 3% of the US population that causes itchy, red, scaly, raised lesions on the skin, most commonly on the elbows, knees, scalp, and back. It can also be associated with other autoimmune diseases and cardiovascular disease. 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).

### TREATING 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 such as psoralen and ultraviolet A radiation (PUVA)
- “Targeted immunomodulators,” such as biologics and apremilast, that address specific markers of inflammation that cause psoriasis symptoms

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, often defined as psoriasis affecting 5%-10% of the body, is generally treated with systemic therapies, phototherapy, and targeted immunomodulators.

### TARGETED IMMUNOMODULATORS AS A TREATMENT OPTION

There are currently 12 targeted immunomodulators available to treat plaque psoriasis. ICER reviewed eight targeted immunomodulators in 2016. This updated review includes four additional therapies and incorporates new data on the existing therapies.

<b>TNF<math>\alpha</math> Inhibitors</b>	Adalimumab (Humira <sup>®</sup> , AbbVie)
	Etanercept (Enbrel <sup>®</sup> , Amgen, Inc.)
	Infliximab (Remicade <sup>®</sup> , Janssen)
	Certolizumab pegol (Cimzia <sup>®</sup> , UCB)*
<b>IL-12/23 Agents</b>	Ustekinumab (Stelara <sup>®</sup> , Janssen)
<b>IL-17 Agents</b>	Brodalumab (Siliq <sup>™</sup> , Valeant Pharmaceuticals and AstraZeneca)
	Ixekizumab (Taltz <sup>®</sup> , Eli Lilly and Co.)
	Secukinumab (Cosentyx <sup>®</sup> , Novartis)
<b>PDE-4 Agent</b>	Apremilast (Otezla <sup>®</sup> , Celgene)
<b>IL-23 Agents</b>	Guselkumab (Tremfya <sup>®</sup> , Janssen/Johnson & Johnson)*
	Risankizumab (Investigational, AbbVie)*
	Tildrakizumab (Ilumya <sup>™</sup> , Sun Pharma)* **

\*Therapy added in 2018 update.

\*\*Not yet on the market as of this publication.

## Clinical Analyses: ICER Evidence Ratings

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### How strong is the evidence that these treatments improve patient outcomes?

- All drugs were found to provide substantial net health benefit compared to placebo.
- In general, **IL-17** agents (brodalumab, ixekizumab, secukinumab) **were found to provide comparable-or-better to incremental net health benefit over TNF $\alpha$  drugs** (adalimumab, etanercept, certolizumab pegol, infliximab), ustekinumab, and apremilast.
- **For IL-23 agents**, ICER found the following:
  - High certainty of a small net health benefit of guselkumab compared to adalimumab
  - High certainty of a small net health benefit of risankizumab compared to ustekinumab
  - Moderate certainty of a comparable or better net health benefit for tildrakizumab compared to etanercept.
  - Evidence was insufficient to distinguish the net health benefit between guselkumab and risankizumab. The net health benefit of tildrakizumab is “comparable or inferior” to that of guselkumab and risankizumab, based on lower levels of clearance of psoriasis lesions.

## Clinical Analyses (continued)

### KEY CLINICAL BENEFITS STUDIED IN CLINICAL TRIALS

#### Psoriasis Area and Severity Index (PASI)

The PASI measures the percent of body surface area with psoriatic lesions on the head, trunk, arms, and legs, as well as the severity of the lesions in each region. In clinical trials, the primary outcome was the proportion of patients achieving “PASI 75,” or a 75% improvement in score.

All targeted immunomodulators showed statistically significantly higher PASI 75, PASI 90, and PASI 100 response rates in comparison to placebo at the end of the induction period.

In direct comparison trials:

- Ustekinumab, secukinumab, ixekizumab, tildrakizumab, and certolizumab pegol were superior to etanercept.
- Secukinumab, brodalumab, ixekizumab, and risankizumab\* were superior to ustekinumab.
- Guselkumab was superior to adalimumab.

*\*Risankizumab data is unpublished and based on grey literature*

In ICER’s network meta-analysis, a technique that combines direct and indirect evidence, the IL-17 and IL-23 agents generally performed better than other classes. Among all drugs, the likelihood of drugs achieving PASI 75 was ranked as follows\*:

**Risankizumab,  
Ixekizumab,  
Guselkumab,  
Brodalumab,  
Secukinumab,  
Infliximab**



**Adalimumab,  
Ustekinumab,  
Certolizumab pegol,  
Tildrakizumab**



**Etanercept,  
Apremilast**

*\*Therapies within each grouping above were not statistically different from each other. See report for full details on indirect comparisons.*

Results on other measures, including the **Physicians’ Global Assessment (PGA)** and the **Dermatology Life Quality Index (DLQI)** closely followed the PASI response results.

The PGA is a physician-scored tool that measures psoriasis severity, and the DLQI is a ten-question survey covering symptoms, feelings, daily activities, and other areas.

## Clinical Analyses (continued)

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### HARMS

Severe or serious adverse events were rare during treatment. Nasopharyngitis, upper respiratory tract infections, and headaches were the most common side effects noted during the trials of certolizumab pegol, guselkumab, risankizumab, and tildrakizumab. There was no indication of increased rates of serious infections, malignancies, and major cardiovascular events for any of the agents.

### SOURCES OF UNCERTAINTY

- Although either PASI 75 or PASI 90 was reported as the primary endpoint in all studies, other clinical outcomes (such as PGA, DLQI, and measures of symptom control) were inconsistently reported across trials making cross-drug comparisons difficult on outcomes important to patients.
- There were limited head-to-head comparisons of the drugs of interest, therefore our network meta-analyses of PASI response are largely driven by indirect evidence; however, our findings are consistent with the results of other recent assessments of the evidence.
- Longer-term data on both drug effectiveness and harms were variable, and we could only confidently compare the efficacy of targeted immunomodulators at the end of the clinical trial period.
- Trials prohibited use of non-study treatments, which does not reflect clinical practice.
- Subgroup data were primarily reported in conference abstracts and the interventions were only compared statistically to placebo, thereby limiting our understanding of how outcomes may differ across population types.

## Economic Analyses

### LONG-TERM COST-EFFECTIVENESS AT LIST PRICE

#### Do targeted immunomodulators meet established thresholds for long-term cost-effectiveness?

For each of the targeted therapies, ICER used the cost per quality-adjusted life year (QALY) gained to calculate the long-term cost-effectiveness of the targeted agents compared to non-targeted treatments. The cost per QALY range that is generally accepted as “reasonable” value in the US is \$50,000–\$150,000.

Neither tildrakizumab nor risankizumab was included in ICER’s model, as prices are not yet available for these agents.

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

Using net prices in 2016, most drugs were well within, if not below, the cost-effectiveness range, representing good long-term value for money.

Using net prices in 2018, the cost-effectiveness for each therapy became less favorable. This change is due in part to increases in net prices between 2016–2018, but the results are not directly comparable due to changes in some model inputs such as the use of different drug discount types and quality of life measures.

Half of the treatments remained within the range for cost-effectiveness, while half, including the two newly included agents for which economic analyses were conducted, exceeded commonly-accepted thresholds.

Treatments	Cost per QALY Gained 2018 Update
Brodalumab	\$131,000
Infliximab	\$134,000
Apremilast	\$135,000
Ixekizumab	\$142,000
Secukinumab	\$145,000
Guselkumab	\$161,000
Adalimumab	\$164,000
Ustekinumab	\$169,000
Etanercept	\$175,000
Certolizumab pegol	\$188,000

## Economic Analyses (continued)

### VALUE-BASED PRICE BENCHMARKS

**What is a fair price for targeted immunomodulators based on their value to patients and the health care system?**

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

Discounts needed to achieve value-based price benchmarks were calculated based on list prices. In contrast to the 2016 report, all of the drugs in 2018 would require discounts from list price to reach value-based price benchmarks. As no WAC is available for risankizumab or tildrakizumab, we calculated only the price to reach the cost-effectiveness thresholds.

	Drug	Annual Value-Based Price Benchmarks	2018 Change from WAC to Reach Benchmark	Net price within benchmark range?
TNF $\alpha$ Inhibitors	Adalimumab	\$25,700–\$39,800	37% to 60% Discount	✗
	Etanercept	\$18,500–\$35,400	44% to 71% Discount	✗
	Infliximab	\$18,800–\$35,000	8% to 51% Discount	✓
	Certolizumab pegol	\$25,500–\$39,700	43% to 63% Discount	✗
IL-12/23 Agents	Ustekinumab	\$25,200–\$37,800	35% to 57% Discount	✗
IL-17 Agents	Brodalumab	\$28,200–\$41,500	9% to 38% Discount	✓
	Ixekizumab	\$27,100–\$39,700	41% to 60% Discount	✓
	Secukinumab	\$25,500–\$39,400	36% to 59% Discount	✓
PDE-4 Agent	Apremilast	\$17,500–\$36,600	8% to 56% Discount	✓
IL-23 Agents	Guselkumab	\$28,400–\$41,500	37% to 57% Discount	✗
	Risankizumab	\$28,800–\$42,100	N/A	N/A
	Tildrakizumab	\$24,900–\$39,800	N/A	N/A

## Economic Analyses (continued)

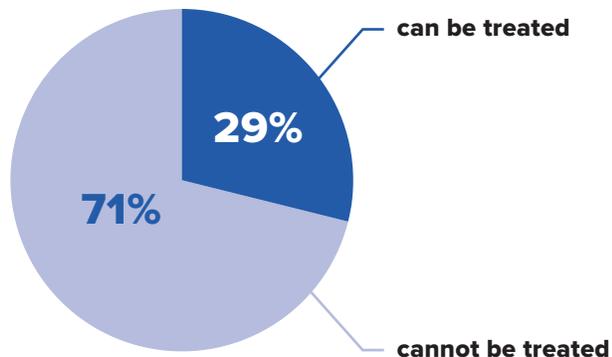
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### POTENTIAL SHORT-TERM BUDGET IMPACT AT LIST PRICE

**How many patients could be treated with targeted immunomodulators before crossing a \$915 million budget impact threshold?**

Potential budget impact was calculated for a population of patients with moderate-to-severe plaque psoriasis being treated with a biologic agent for the first time.

In the 2018 update, the potential budget impact for certolizumab pegol and guselkumab surpassed ICER's budget threshold of \$915 million. At estimated net prices, only 29% of the eligible population could be treated with either agent before reaching the threshold. Potential budget impact was not calculated for risankizumab or tildrakizumab as prices were not available at the time of the report.



## Voting Results

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The New England CEPAC deliberated on key questions raised by ICER's report at a public meeting on July 12, 2018. More detail on the voting results is provided in the [full report](#).

*Evidence was reviewed for patients with moderate-to-severe plaque psoriasis for whom treatment with topical therapies, older systemic therapies, and/or phototherapy has been ineffective, contraindicated, or not tolerated.*

The panel voted the evidence was sufficient to show a superior net health benefit of guselkumab, and, assuming that evidence presented in grey literature is consistent with the final published results, of risankizumab, compared to TNF $\alpha$  inhibitors. Evidence was inadequate to show a net health benefit of certolizumab pegol over the other TNF $\alpha$  inhibitors (adalimumab and etanercept) or of tildrakizumab over the subcutaneous TNF $\alpha$  inhibitors.

### OTHER BENEFITS

Council members identified several potential benefits beyond those studied in clinical trials, including reduced complexity, reduced caregiver or family burden, improved ability to return to work or other activities, and the therapies' novel mechanism of action, meaning that the treatments may be effective in patients for whom other therapies have failed. Council members also noted that the new therapies may reduce stigma faced by those with psoriasis, and reduce feelings of anxiety or frustration.

### CONTEXTUAL CONSIDERATIONS

Council members also voted that the high severity of plaque psoriasis in terms of quality of life, the high lifetime burden of illness, and the uncertainty around the long-term risks and benefits of the therapies were important contextual considerations.

### LONG-TERM VALUE FOR MONEY

A majority of the panel judged the long-term value for money of treatment with guselkumab to be "intermediate" compared with non-targeted therapy. Treatment with certolizumab pegol, compared to non-targeted therapy, was found to provide low long-term value for money, due to its high price and a lack of evidence suggesting that it is better than other therapies in its class.

## Key Policy Implications

The 2016 policy recommendations were updated in a moderated discussion of the New England CEPAC. Recommendations marked with an asterisk (\*) are updated based on the 2018 Condition Update. All other recommendations remain unchanged from 2016.

This discussion was supported by input from a clinical expert and a patient advocate representative. None of the statements below should be taken as a consensus view held by all participants. More detail is provided in the [full report](#).

### PAYERS

#### Consider limiting or abolishing step therapy approaches to coverage.\*

Despite reasonable cost-effectiveness for several agents, step therapy continues to be the dominant approach among most insurers. Patients and clinicians continue to reiterate that such protocols delay improvements to patients' quality of life.

#### 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.

#### Coverage Policy Example: Express Scripts

According to industry experts, some best practices that have emerged since 2016. Leaders at Express Scripts have said they sought to renegotiate contracts with the manufacturers of all targeted immunomodulators with a psoriasis indication, the goals being to eliminate all step therapy for treatment of a psoriasis diagnosis and establish a formulary with an equal co-payment structure for all drugs for treating psoriasis (see more details [here](#)). Negotiations have been successful for most targeted psoriasis drugs, and have included provisions to refund payers the cost of treatment for patients who discontinue their chosen therapy early. For those psoriasis therapies that have not been brought into this contract approach, however, step therapy requirements and higher cost-sharing structures remain.

### MANUFACTURERS

**Foster transparency in the rationale for price increases.\*** Manufacturers should keep prices at levels that reflect the added benefit to patients, be mindful of the impact on health care costs of the growing use of targeted immunomodulators, and recognize the potential for increased patient access linked to lower prices. In 2016, ICER's report noted that some of the classes of psoriasis drugs had seen significant price increases on a year-over-year basis, and these increases have continued.

## Key Policy Implications (continued)

### PATIENT ADVOCACY ORGANIZATIONS

Lead research efforts to evaluate heritability of psoriasis and the impact of managing plaque psoriasis on caregivers and families.

### RESEARCHERS AND MANUFACTURERS

Conduct research that directly compares real-world treatment options and sequential treatment effectiveness for both naïve and treatment-experienced patients.

Converge on a single metric for patient reported psoriasis specific outcomes for trials.

**Generate additional information on the treatment durability of IL-17 and IL-23 agents.\***

### SPECIALTY SOCIETIES

**Update treatment guidelines for patients with moderate-to-severe chronic plaque psoriasis in a form that is easy to understand and easy-to-use by payers, clinicians, and patients.** \* In 2016, payers expressed frustration with out-of-date clinical guidelines that precede the introduction of IL-17 agents. The need for revised treatment guidelines is now even more urgent considering the availability of the IL-23 agents, and the approval of certolizumab pegol for use during pregnancy.

The National Psoriasis Foundation and American Academy of Dermatology are collaborating to update clinical practice guidelines for psoriasis with a release anticipated within the coming year.

### 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.

## 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)).