NEW ENGLAND CEPAC
COMPARATIVE EFFECTIVENESS PUBLIC ADVISORY COUNCIL
AN ICER PROGRAM

Targeted Immunomodulators for the Treatment of Moderate-to-Severe Plaque Psoriasis

Condition Update
Modeling Analysis Plan

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Institute for Clinical and Economic Review

ICER
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1. Approach

The primary aim of this analysis will be to estimate the cost-effectiveness of targeted treatments for plaque psoriasis in patients who have failed phototherapy and/or methotrexate. The analysis considers eleven drugs which can be divided into five categories: tumor necrosis factor (TNF) inhibitors, interleukin (IL)-12/23 inhibitors, IL-17A inhibitors, IL-23 inhibitors, and phosphodiesterase (PDE)-4 inhibitors.

Clinical and economic outcomes will be evaluated using a Markov model programmed in Microsoft Excel used in our previous analysis of treatments for plaque psoriasis and which formed the basis of our previously reported model on targeted treatments for plaque psoriasis. The model will use a health system perspective, focusing on direct medical costs. Productivity gains associated with clinical resolution of psoriasis will be included in a scenario analysis reflecting a modified societal perspective. In order to facilitate comparison with published studies in this disease area, the model will use a 10-year time horizon. The standard 3% discount rate will be applied to costs and outcomes. Clinical success of treatment will be evaluated using the Psoriasis Area Severity Index (PASI), a clinician-reported outcome measure indicating severity of plaque psoriasis by body area. We propose to evaluate three outcomes: quality-adjusted life years (QALYs), months spent in health states of PASI 75 or greater, and months spent in health states of PASI 90 or greater.

2. Methods

2.1 Overview and Model Structure

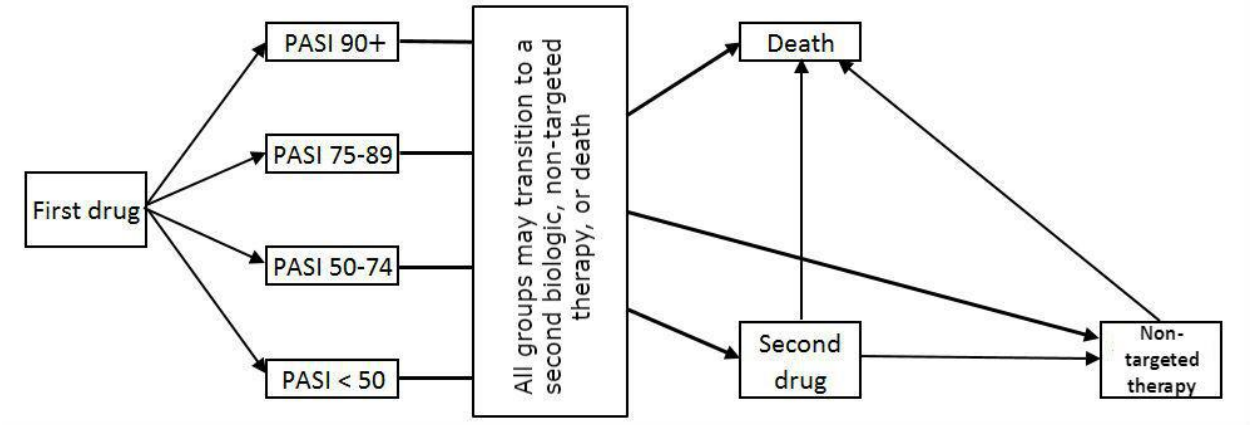
The model will be a Markov model, similar to that used in ICER's previous evaluation in plaque psoriasis. The model is based on the York model[1] that was established for use in NICE evaluations of anti-psoriasis drugs; the York model has provided the basis for many cost-effectiveness analyses in plaque psoriasis, including ICER's 2016 report on targeted treatments for plaque psoriasis. While the York model uses weighted averages of utility among all clinical responders, the proposed model makes these health states explicit, and adds states for death and a second-line biologic. This explicit accounting of health states will be useful for estimating outcomes other than the QALY, while the inclusion of second-line treatment allows us to more closely model clinical practice and to explore the uncertainty surrounding the impact of a first-line biologic drug on the effectiveness of subsequent biologics.

Patients are distributed into different health states defined by PASI response level (Figure 1), as informed by the results of the ongoing network meta-analysis. Patients remain on first-line treatment for the duration of the label-indicated induction period, after which point patients with a clinical response less than PASI 75 discontinue first-line treatment, and patients in the PASI 75-89

and PASI 90-100 health states face a monthly probability of discontinuation. Specifically, duration of response and the effect of adverse events on discontinuation will be combined into a drug-specific probability of first-line targeted treatment discontinuation, which will vary by year (including the first year after treatment induction). Patients cannot transition between PASI health states within the model.

Once discontinuing first-line targeted treatment, patients may start a second targeted treatment or restart non-targeted treatment (e.g., topical treatments, phototherapy, methotrexate). Second-line targeted treatment will be defined as one of several baskets composed of other drugs due to the paucity of data on second line treatment effectiveness for specific drug sequences. We currently propose the following allocation of patients to second-line baskets based on their first-line treatment: patients on IL-17 drugs will transition to a basket of IL-23 drugs; patients on IL-23 drugs will transition to a basket of IL-17 drugs; and patients on any other class of drug will transition to a market basket including all drugs in both the IL-17 and IL-23 classes. Patients on second-line targeted treatment will have a non-drug-specific probability of discontinuing to non-targeted treatment, and all patients have a probability of death which, due to the absence of evidence that risk of death can be modified by resolution of psoriasis symptoms, is exclusively age-dependent.

Figure 1. Model Framework



2.2 Target Populations

The population of focus for this review will be patients with moderate to severe plaque psoriasis who have failed treatment on phototherapy and methotrexate. Based on evaluation of the populations included in each drug's pivotal trials, the mean age of the population will be set to 45 years, which will inform the model's mortality rate, and the mean weight will be set to 90 kg, which will inform the dosing of some included drugs.

Depending on the availability of data, we may perform a separate analysis on a subgroup of patients who have taken previous biologic medicines for the treatment of plaque psoriasis.

2.3 Interventions

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers on which treatments to include. Drugs that are new to this psoriasis evaluation update are **bolded**. The full list of interventions is as follows:

- TNF inhibitors
    - adalimumab (Humira®)
    - **certolizumab pegol (Cimzia®)**
    - etanercept (Enbrel®)
    - infliximab (Remicade®)
- IL-17A inhibitors
    - secukinumab (Cosentyx®)
    - ixekizumab (Taltz®)
    - brodalumab (Siliq®)
- IL-12/23 inhibitor
    - ustekinumab (Stelara®)
- IL-23 inhibitors
    - **guselkumab (Tremfya®)**
    - **tildrakizumab (investigational)**
- Phosphodiesterase-4 inhibitor
    - apremilast (Otezla®)

Comparators

The drugs will be compared both to non-targeted treatment and to all other drugs.

2.4 Key Model Choices and Assumptions

Table 1. Key Model Assumptions

Assumption	Rationale
Each group will have an annual probability of discontinuation or treatment failure, which can be unique to each drug.	The effectiveness of a given drug can be assessed not only by the probability of achieving clinical response, but also by the longevity of that response. Therefore, we integrated discontinuation for any cause, including loss of effectiveness and adverse events, into the per-cycle discontinuation rate for each drug.
After discontinuation from first-line targeted treatment, 50% of patients continue to a market basket of second-line targeted treatments and the other 50% receive non-targeted treatment.	A study using data among commercially insured patients from 2010 through 2011 found that approximately 50% of patients who failed a first-line targeted treatment did not continue onto a second targeted treatment.2 This estimate will be updated as needed and as new evidence is evaluated.
The effectiveness of the second-line biologic agent will not be calculated for each possible combination of first- and second-line agents. Rather, 2nd-line biologic effectiveness will be calculated by averaging the probability of achieving a clinical response (PASI 75+ and PASI 90+) within defined second-line drug baskets.	We created baskets of likely second-line agents rather than including every possible combination of first- and second-line targeted treatments due to a paucity of effectiveness data for second-line treatment.
The effectiveness of the second-line market baskets is reduced by 10 percentage points (e.g., the probability of having a response of PASI 90-100 is decreased by 5 percentage points and the probability of having a response of PASI 75-89 is decreased by 5 percentage points, with identical increases in the probability of achieving PASI 50-74 and PASI <50) compared to first-line targeted treatment.	There is significant ambiguity around the impact of first-line biologic treatment on subsequent biologic treatments, however some clinical evidence points to a roughly 10% lower effectiveness among second-line targeted drugs.3-5 This estimate will be updated as needed as new evidence is evaluated.
Health state utilities will be assigned to each PASI score category, regardless of the drug that is being modeled.	Drug-specific utility data is not available. PASI score can be considered a surrogate marker of health-related quality of life, albeit one that does not include utility impacts of drug administration or adverse effects.
Probability of death is related to age only.	There is no evidence indicating that risk of death is modified by resolution of plaque psoriasis symptoms.
Adverse effects are not included in the base case but may be included in subgroup analyses.	Previously published cost-effectiveness analyses largely exclude adverse events. To assure comparability with these prior analyses, adverse effects are also excluded from this model. Sensitivity analyses may evaluate the effect of select adverse events. The effect of adverse events on drug discontinuation are included.

2.5 Input Parameters

Clinical Inputs

The estimated effectiveness of each drug will be gathered from a network meta-analysis of published trials and unpublished data from manufacturers. Effectiveness will be measured via the PASI score. Four groups of patients will be defined by their PASI scores: 90 to 100; 75 to 89; 50 to 74; and less than 50. A PASI score of 75 or greater is considered adequate response; a PASI score between 50 and 74 is considered partial response.

Transition Probabilities/Response to Treatment

Probability of initial assignment to a given PASI response grouping will be taken directly from the results of the NMA. Patients cannot transition between PASI health states within the model. Drug-specific discontinuation rates will be derived from studies of short- (e.g., 6 months to 1 year) and long-term discontinuation rates from targeted treatment among plaque psoriasis patients.[6,7] Age-specific mortality rates come from the U.S. Social Security Administration life tables.

Health State Utilities

Health state utility weights will be assigned to each PASI score category. They will be taken from a regression-based analysis of secukinumab performed for NICE[8] in which EQ-5D quality of life assessments were answered by psoriasis patients alongside PASI assessments (Table 3). The utility for non-targeted therapy will be set to equal the baseline utility of these patients and will be varied in scenario and/or sensitivity analyses to explore the impact of uncertainty in this estimate, which was previously found to be highly influential on study results. We will also explore the impact of using different utility sets. A separate health state utility for PASI 100 vs. 90-99 will not be included, as ICER's previous analysis showed this did not have a meaningful impact on results.

Utility for second-line drug baskets will be derived from the average of the probabilities of achieving each health state for the included drugs, reduced by ten percentage points as described above.

Table 2. Utility Values for Health States

Health state	Utility value
PASI 90-100	0.90
PASI 75-89	0.87
PASI 50-74	0.83
PASI < 50	0.75
Non-targeted therapy	0.64

Drug/Therapy Utilization

Table 3. Dosage regimen for each drug

Drug	Initiation period	Maintenance period
Adalimumab	80 mg once	40 mg every other week starting one week after initial dose
Apremilast	5-day titration up to 30 mg 2x/day	30 mg 2x/day
Brodalumab	N/A	210 mg every 2 weeks
Certolizumab pegol	TBD	TBD
Etanercept	50 mg 2x/week for 3 months	50 mg 1x/week
Guselkumab	100 mg at weeks 0 and 4	100 mg every 8 weeks
Infliximab	5 mg/kg at weeks 0, 2, and 6	5 mg/kg every 8 weeks
Ixekizumab	160 mg at week 0, then 80 mg at weeks 2, 4, 6, 8, 10, and 12	80 mg every 4 weeks
Secukinumab	300 mg at weeks 0, 1, 2, 3, and 4	300 mg every 4 weeks
Tildrakizumab	TBD	TBD
Ustekinumab	Patients ≤100kg/>100kg: 45mg/90mg at weeks 0 and 4	Patients ≤100kg/>100kg: 45mg/90mg every 12 weeks

N/A = not applicable; TBD = to be determined

Adverse Events

To ensure comparability with most previously published cost-effectiveness analyses, this analysis has not included adverse events in the base case analysis. The included drugs have low rates of adverse events and generally only include infection. However, a sensitivity analysis will be performed in order to account for serious adverse effects that are disproportionately present in certain drugs, such as the risk of upper respiratory infection with infliximab or the risk of suicide with brodalumab. The effect of adverse events on drug discontinuation are accounted for in all scenarios.

Cost Inputs

Drug Acquisition Costs (Table 5)

Net prices for each drug will be calculated by subtracting a class-specific rebate percentage (calculated as the average of discounts for drugs in each class, rounded to the nearest 5%) from the WAC, as derived from records of purchases and reported by SSR Health.[9] As of January 30, 2018, these rebate percentages were: TNF-α (35%, for certolizumab pegol, etanercept, and infliximab), IL-12/23 (20%, ustekinumab), IL-17 (40%, secukinumab, ixekizumab, and brodalumab), and PDE-4 (20%, apremilast); these estimates will be updated. Infliximab is dosed by weight. We will assume that vials will not be shared between patients and therefore round up to the cost of six 80 mg vials. We will estimate that 30% of patients weigh greater than 100 kg and will therefore receive the 90 mg dose of ustekinumab rather than the 45 mg dose.

Table 4. Drug Cost Inputs

Intervention	Administration	Unit	WAC per Unit/Dose	Class-Specific Discount	Net Price per Unit/Dose
Adalimumab	SC	40 mg	$2,436.02	35%	$1,583.41
Apremilast	Oral	30 mg	$51.67	20%	$41.34
Brodalumab	SC	210 mg	$1,750.00	40%	$1,050.00
Certolizumab pegol	SC	200 mg	$4,044.32	35%	$2,628.81
Etanercept	SC	50 mg	$1,218.00	35%	$791.70
Guselkumab	SC	100 mg	$10,158.52	NA	TBD
Infliximab	IV	100 mg	$1,167.82	35%	$759.08
Infliximab-abda	IV	100 mg	$753.39	35%	$489.70
Infliximab-dyyb	IV	100 mg	$946.28	35%	$615.08
Ixekizumab	SC	80 mg	$4,777.35	40%	$2,866.41
Secukinumab	SC	300 mg	$4,712.38	40%	$2,827.43
Tildrakizumab	SC	100 or 200 mg	TBD	TBD	TBD
Ustekinumab	SC	45 mg	$10,292.15	20%	$8,233.72
		90 mg	$20,584.30	20%	$16,467.44

*WAC from REDBOOK as of January 30,2018

**For investigational drugs, no annual cost was assumed except the cost needed to achieve thresholds.

Administration and Monitoring Costs

Patients taking a drug administered orally will be assumed to have no administration-related costs. Patients taking a drug administered subcutaneously will be assumed to incur the cost of one additional clinic visit at which instruction takes place, after which they self-administer the drug. Patients taking an intravenously-administered drug incur the cost of two hours at an infusion

center, to which the lost productivity from one missed day of work will be added. For provider-administered drugs, we will add a mark-up to the drug acquisition cost. The monthly cost for administration of second-line therapy will be estimated by averaging the monthly administration costs for all relevant first-line drugs during their maintenance phases.

Many drugs included in this study require that patients have laboratory tests prior to and/or during treatment. We therefore add to the cost of treatment the following tests for each drug (Table 6).

Table 5. Laboratory regimens for anti-psoriasis drugs

Drug	Latent TB	Active TB	CBC	HBV	LFT	Renal
Adalimumab			Twice yearly	Once, at initiation	Quarterly	
Apremilast						Once, at initiation
Brodalumab						
Certolizumab pegol	TBD	TBD	TBD	TBD	TBD	TBD
Etanercept	Once, at initiation	Quarterly	Twice yearly	Once, at initiation	Quarterly	
Guselkumab	TBD	TBD	TBD	TBD	TBD	TBD
Infliximab	Once, at initiation	Twice yearly	Twice yearly			
Ixekizumab	Once, at initiation	Twice yearly				
Secukinumab	Once, at initiation	Twice yearly				
Tildrakizumab	TBD	TBD	TBD	TBD	TBD	TBD
Ustekinumab	Once, at initiation	Twice yearly	Twice yearly			

TBD = to be determined

Health Care Utilization Costs

Each patient will be assumed to have one clinic visit per quarter, regardless of treatment strategy used.

Adverse Event Costs

In scenario analysis only, hospitalization for pneumonia will be valued at $5,873 based on Medicare reimbursement rates.

Productivity Costs

Productivity costs will not be included in the main analysis but will be explored in a scenario analysis. As derived from studies of productivity included in the randomized controlled trials for adalimumab[10] and ixekizumab[11], we will assume that a patient achieving PASI 75 or greater on a first targeted drug will improve their productivity by $4,900. Due to the estimated decrease in effectiveness associated with second-line targeted treatments, we will decrease this by 10% to $4,400 for patients achieving PASI 75 or greater on their second targeted treatment.

2.6 Model Outcomes

Time spent in each health state will be weighted according to the health state utilities described above in order to calculate the QALYs attributable to each treatment. In addition, we will also compare months spent in health states of PASI≥75 and PASI≥90 for each of the drugs. There will be no difference in survival between medications since mortality is related to age alone.

2.7 Analysis

Each model cycle lasts one month. Survival by PASI response category, quality-adjusted survival, and health care costs will be estimated for each model cycle and then summarized over a ten-year time horizon for each treatment option, with the potential of also including a lifetime time horizon. Differences in outcomes (QALYs, months in PASI≥75, and months in PASI≥90) and costs between each treatment and comparator will be used to calculate incremental cost-effectiveness ratios.

Sensitivity Analyses

We will conduct one-way sensitivity analyses to identify the key drivers of model outcomes for select pairs of drugs, using available measures of parameter uncertainty (i.e. standard errors) or reasonable ranges for each input described in the model inputs section above. Probabilistic sensitivity analyses will also be performed by jointly varying all model parameters over 5,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results.

In the probabilistic sensitivity analysis, we will use the following distributions: Dirichlet for assignment to PASI response category, beta for utility weights and discount rate, normal or lognormal for costs, and normal for patient age and weight. Additionally, we will perform a threshold analysis by systematically altering the price of each drug to estimate the maximum prices that would correspond to willingness to pay (WTP) thresholds of $50,000, $100,000 and $150,000 per QALY.

Scenario Analyses

We propose including the following scenario analyses, with inclusion of each being dependent on availability of data:

1. Including productivity offsets for patients achieving clinical remission of plaque psoriasis.
2. Varying the rate of second-line targeted treatment among patients who fail first-line targeted treatment from 25% to 75%.
3. Using WAC drug prices rather than discounted net prices.
4. Using a lifetime horizon.
5. Including the cost of hospitalization for pneumonia.
6. Assuming a higher utility for non-targeted treatment health state
7. Including the outcome impacts of suicide among brodalumab patients.
8. Subgroup analysis for patients who have taken previous biologic drugs for treatment of plaque psoriasis.

Model Validation

We will use several approaches to validate the model. First, we will provide preliminary methods and results to manufacturers, patient groups, and clinical experts. Based on feedback from these groups, we will refine data inputs used in the model, as needed. Second, we will vary model input parameters to evaluate face validity of changes in results. We will perform model verification for model calculations using both internal and external reviewers. Finally, we will compare results to other cost-effectiveness models in this therapy area.

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