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Driving Health Sector Innovation
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Deliverable 3: Part 2
ASSESSMENT OF ETANERCEPT (ENBREL®, AMGEN, INC.)

1) What is the assessment of ICER regarding this drug's comparative effectiveness?

According to ICER's report, when evaluating based on the Psoriasis Area and Severity Index (PASI):

- All of the targeted immunomodulator therapies showed statistically significantly higher PASI 75, 50, 90, and 100 response rates compared to placebo at the end of the induction period (10-16 weeks depending on the agent).
- In direct head-to-head trials, ustekinumab, secukinumab, and ixekizumab demonstrated superior PASI 90 and 100 response rates compared to etanercept.
- Secukinumab and brodalumab were superior to ustekinumab for PASI 90 and 100 responses.
- An unpublished head-to-head trial (IXORA-S) showed ixekizumab had statistically significant benefit over etanercept on all key PASI measures.

So in summary, while all the targeted immunomodulators showed clinically meaningful PASI responses compared to placebo, several agents like the IL-17 inhibitors secukinumab and ixekizumab demonstrated superior skin clearance rates directly compared to etanercept based on the higher PASI 90/100 thresholds in ICER's comparative effectiveness analysis.(Page 7-8)

a. What metrics does ICER use to evaluate the drug's comparative effectiveness?

The key metrics ICER used to evaluate the comparative clinical effectiveness of Enbrel (etanercept) included:

- Psoriasis Area and Severity Index (PASI) scores: Specifically the PASI 50, 75, 90 and 100 response rates, which measure the proportion of patients achieving those percentage reductions in PASI score from baseline.
- Physician's Global Assessment (PGA) or Investigator's Global Assessment (IGA): Assessments by clinicians of overall disease severity and improvement.
- Dermatology Life Quality Index (DLQI): A patient-reported measure of how psoriasis impacts quality of life.
- Other patient-reported outcomes: Such as the Short Form-26 for general quality of life, Visual Analog Scales, and the Psoriasis Symptom Inventory to evaluate symptom control.

To evaluate potential harms and tolerability, ICER analyzed:

- Treatment-related adverse event rates, including rates of infections
- Discontinuation rates due to adverse events as a measure of treatment tolerability

So in summary, ICER used a range of clinical outcome measures focused on physician assessments of skin clearance, patient-reported quality of life and symptoms, as well as safety data - all aimed at comprehensively evaluating the comparative clinical effectiveness of the drug versus other treatments based on trial data.

2) What is the assessment of ICER regarding this drug's cost effectiveness?

According to figure 6 on the ICER report the QALYs point out the differences between the psoriasis drugs. **Etanercept QALYs are below adalimumab, infliximab, secukinumab, brodalumab, ixekizumab, ustekinumab**. In terms of cost, **Etanercept is the third cheapest** while consistently being the **third least effective**.
To be more specific, etanercept QALYs can be extracted from the 10yr cost in figure 6 and the 1st year therapy cost present on table 17 can be used to assess short term costs. In this table, etanercept has one of the top costs in comparison to the competition.

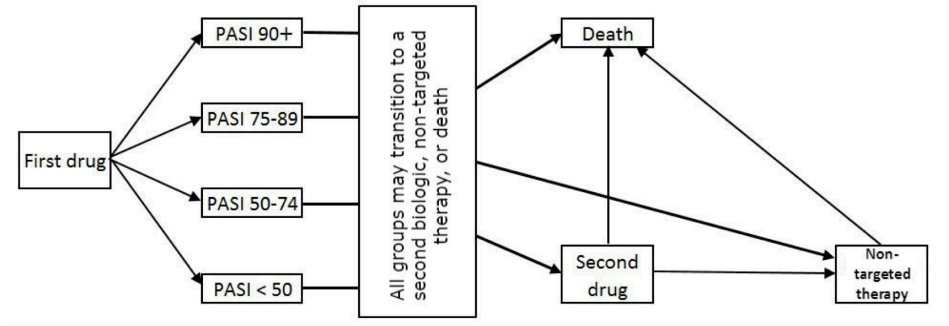
Treatment	Unit cost	Cost of initiation period	Monthly cost of maintenance	Cost of 1st year of therapy	Source
adalimumab (per 40mg)	$1,434	$14,361 (4 mo.)	$2,868	$37,305	Net price calculation*
apremilast (per 30mg)	$34	$7,549 (4 mo.)	$1,931	$22,997	Net price calculation
brodalumab (per 210mg)	[$2,560]	[$17,969] (3 mo.)	[$2,560]	[$41,009]	Assumed average of ixekizumab and secukinumab, with IL-17A discount
etanercept (per 50mg)	$717	$17,283 (3 mo.)	$2,868	$43,095	Net price calculation
infliximab (per 100mg)	$779	$16,874 (10 wks.)	$1,948	$35,380	Net price calculation
ixekizumab (per 80mg)	$2,681	$21,523 (3 mo.)	$2,681	$45,652	Net price calculation
secukinumab (per 300mg)	$2,439	$14,656 (3 mo.)	$2,439	$36,607	Net price calculation
ustekinumab (70% 45mg/30% 90mg)	$7,514	$26,072 (3 mo.)	$3,256	$55,376	Net price calculation
2nd line targeted drug (per cycle)	$2,569	$8,272** (1 mo.)	$2,569	$36,531	Average monthly cost of above drugs
non-targeted therapy (per cycle)	$820	n/a	$820	n/a	Yu, Curr Med Res Opin 2009 (inflated to 2016 dollars using medical cost inflation rate)[137]

(*page 60 table 17*)

a. What metrics does ICER use to evaluate the drug's cost effectiveness? How does this differ from comparative effectiveness?

ICER used a Markov model with eight health states wherein patients could transition between states every month. Each health state, shown below, had an assumption attached to it around whether a patient was to discontinue therapy, continue with second-line targeted/non-targeted therapy, etc. Costs and effects were averaged across therapies.(*Page 15*)

Figure 5: Markov model of psoriasis treatment and response

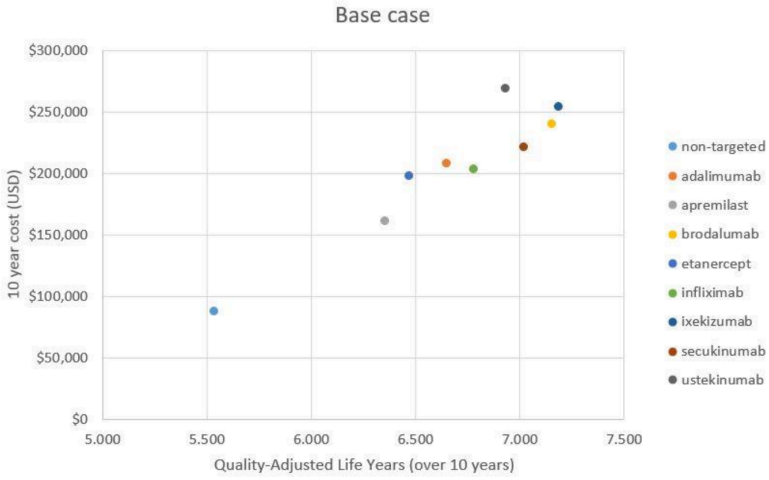


Specific economic inputs to measure cost effectiveness included drug acquisition costs, administration costs, laboratory and clinic visit costs, adverse effects costs, productivity costs. Clinical inputs included utilities and clinical probabilities. ICER's metrics for cost effectiveness differ from comparative effectiveness, as they **focus solely on costs (both economic and clinical)** when compared to Enbrel's competitors, whereas comparative effectiveness focuses mainly on **clinical benefits and harms associated with the drug**.

3) What is the assessment of ICER regarding this drug's 'long term value for money'?

According to figure 6 on the ICER report, the QALYs point out the differences between the psoriasis drugs. Etanercept QALYs are below adalimumab, infliximab, secukinumab, brodalumab, ixekizumab, ustekinumab. In terms of cost, Etanercept is the third cheapest while consistently being the third least effective.

Figure ES2: Cost-effectiveness plane for all comparators (base case)*



a. What metrics does ICER use to evaluate the drug's 'long term value for money'? How does this differ from comparative effectiveness? From cost effectiveness?

The key metrics ICER uses to evaluate a drug's long-term value for money are:

1. Comparative clinical effectiveness over the long-term, typically a patient's lifetime horizon.
2. Incremental cost-effectiveness ratios over the long-term, such as incremental costs per QALY or life year gained.
3. Other potential benefits/disadvantages beyond clinical outcomes.
4. Contextual considerations regarding the disease and treatment landscape.

Evaluating long-term value for money differs from comparative clinical effectiveness assessments by explicitly considering the economic costs required to achieve any improved clinical outcomes identified, in addition to the clinical data itself.

It differs from a standard cost-effectiveness analysis by taking a more comprehensive view incorporating contextual factors beyond just the incremental cost per QALY, and by evaluating over a lifetime rather than shorter time horizon.

ICER's long-term value for money metric aims to provide a holistic assessment of a drug's benefits, risks, costs and other relevant considerations from both a clinical and economic perspective over a patient's lifetime.

For Enbrel/etanercept specifically, ICER evaluated total lifetime medical costs, QALYs, life years gained, incremental cost/QALY ratios compared to other treatments, as well as contextual factors like disease severity and prevalence when assessing its long-term value for money.

4) Does the ICER report recommend a price discount for this drug to better align value for money? If so, by how much?

According to the ICER report, yes, a price discount is recommended for Etanercept (Enbrel) in order to better align its value for money.

Per ICER's methods, the value-based benchmark price range for a drug is defined as the pricing that would achieve incremental cost-effectiveness ratios between $100,000 and $150,000 per quality-adjusted life year (QALY) gained compared to existing therapies.

With the exception of adalimumab, apremilast, and infliximab, all the drugs evaluated in the ICER report, including Etanercept, would require discounts from their current Wholesale Acquisition Cost (WAC) prices to fall within ICER's cost-effectiveness threshold value range.

Specifically for Etanercept 50mg, the ICER report states that a discount of 3% to 45% from its WAC price would be needed to reach ICER's $100,000 to $150,000 per QALY value-based price benchmark range for this therapy.

So in summary, yes the ICER report recommends a discount for Etanercept/Enbrel, with the suggested discount range being 3% to 45% off its current WAC pricing to better align its value for the achieved clinical outcomes based on ICER's cost-effectiveness analysis.

5) If you were a patient eligible for treatment with this disease, would you be pleased with ICER's assessment? Please justify your answer.

If I were a patient eligible for treatment with plaque psoriasis, I would be pleased with ICER's assessment for the following reasons:

From a clinical effectiveness standpoint, ICER found that all of the targeted immunomodulator therapies evaluated showed statistically significant higher response rates compared to placebo, as measured by PASI 75 (75% or better improvement from baseline) at the end of the induction period. The therapies also demonstrated higher PASI 50, 90, and 100 response rates versus placebo. This suggests these medications can provide meaningful clinical benefit.

Regarding safety, ICER's analysis of 1-year follow-up data from pivotal trials indicated the targeted immunomodulators had comparable safety profiles. As a patient, seeing these therapies did not raise additional safety concerns would be reassuring.

From a cost-effectiveness perspective, I would appreciate that ICER's report utilized real-world data and conservative assumptions to analyze the value proposition. For drugs that exceeded conventional cost-effectiveness thresholds based on QALY or PASI outcomes, ICER recommended specific discount ranges from current pricing to better align value. As a patient, having an independent analysis quantifying appropriate pricing for the clinical benefits delivered would be valuable.

Overall, seeing the clinical data synthesis, safety evaluation, and pricing analysis provided by ICER's comprehensive review would give me confidence as a patient that these medications could effectively and reasonably treat my condition. ICER's assessment covers the key aspects I would prioritize when selecting a treatment option.

6) If you were the CEO of the company labeling this product, would you be pleased with ICER's assessment? How might you use ICER's assessment? Please justify your answers.

As the CEO of the company marketing etanercept (Enbrel), I would not be fully pleased with ICER's assessment for a few key reasons:

Clinical Effectiveness Disadvantages: ICER's analysis shows etanercept being rated lower than several competitor products in terms of achieving high levels of skin clearance (PASI 90/100 responses). The newer IL-17A inhibitors demonstrated better clinical efficacy on these stringent measures. As CEO, seeing our product lagging competitors on these clinical endpoints would be concerning.

Worse Cost-Effectiveness: Similarly, ICER's report suggests the IL-17A agents may provide better economic value compared to etanercept based on incremental cost per QALY or PASI response achieved. This raises competitiveness concerns.

However, as CEO I would still try to leverage ICER's report in the following ways:

1. Use it to fully understand potential market criticisms and competitive disadvantages we need to address.
2. Highlight positive differentiators like etanercept's once-weekly dosing compared to more frequent dosing required for some competitors.
3. Note that while ICER deems etanercept higher cost, their recommended 3-45% discount range could improve cost-effectiveness alignment.
4. Leverage ICER's assessment of comparable safety profiles as a positive factor.

So in summary, while certainly not ideal, I would use ICER's assessment to understand our drug's perceived weaknesses, but also promote its remaining advantages and adopt their pricing recommendations to improve cost-effectiveness and overall market positioning.

7) If you were an insurer, how might you use ICER's assessment?

As an insurer, leveraging ICER's assessment can be invaluable in guiding decisions regarding drug coverage. In the case of ustekinumab, secukinumab, ixekizumab, and Etanercept, ICER's assessment highlights significant differences in clinical effectiveness, with the former three demonstrating superiority for PASI 90 and 100, particularly with ixekizumab showing the highest relative effectiveness. Despite Etanercept being rated lower by ICER (C-) due to moderate certainty of inferior net health benefit, its lower cost presents a compelling factor for consideration.

As an insurer, I would weigh ICER's assessment alongside other factors such as safety profiles and cost differentials. While Etanercept may be deemed less effective by ICER, its affordability could make it a preferred option in certain scenarios. Additionally, armed with information about more cost-effective alternatives, I would collaborate with healthcare providers to incentivize the use of the most efficient drugs through rebates or other reimbursement strategies. This aligns with value-based care principles, where performance and healthcare outcomes are tied to reimbursement, fostering a more sustainable and efficient healthcare ecosystem.