

## Summary

### WHAT IS RHEUMATOID ARTHRITIS?

Rheumatoid Arthritis (RA) is the most common chronic inflammatory arthritis in adults, affecting between 1.3 and 1.8 million Americans. Symptoms of RA commonly include morning stiffness and joint swelling of the feet, hands, and knees. If not well-controlled, RA can lead to permanent joint damage and deformity.

### TREATMENT OPTIONS

Patients with moderately-to-severely active RA who have had an inadequate response to conventional disease-modifying anti-rheumatoid drugs (cDMARDs) are commonly treated with a biologic or small-molecule drug targeted at mediators of inflammation in RA. These targeted agents are collectively referred to as targeted immune modulators (TIMs), and are often used in combination with a cDMARD such as methotrexate.

While most TIMs are biologic agents that require subcutaneous injection or intravenous infusion, three oral small molecule janus kinase (JAK) inhibitors have received FDA approval for use in RA: upadacitinib (**RINVOQ™**, AbbVie), tofacitinib (**Xeljanz®**, Pfizer), and baricitinib (**Olumiant®**, Lilly).

A biosimilar is a biologic drug that is highly similar in structure and function to a licensed reference product. The FDA requires that manufacturers demonstrate that there are no clinically meaningful differences in safety, purity, and potency between the biosimilar and the reference product. Many of the biologics used to treat RA have FDA-approved biosimilars.

### KEY REPORT FINDINGS

- In patients with moderately-to-severely active RA who have had an inadequate response to cDMARDs, upadacitinib and tofacitinib provide substantial net health benefits compared to cDMARDs and a comparable or better net health benefit compared to adalimumab.
- Due to inconsistent endpoint measurement and trial design, we were unable to compare the JAK inhibitors to each other.
- Upadacitinib achieved common thresholds for cost-effectiveness compared to adalimumab. However, ICER's [2017 review of treatments for rheumatoid arthritis](#) found that adalimumab itself may be priced above commonly cited cost-effectiveness thresholds.
- Baricitinib's indication does not include the TIM naïve population, therefore it was not evaluated in ICER's review.
- Biosimilars, such as infliximab-dyyb, are as safe and effective as their reference biologic.

### KEY POLICY RECOMMENDATIONS

- In a dysfunctional market system, in order to protect patients today and improve their future access to innovative therapies, policy makers may need to consider some form of regulatory intervention to ensure that drug prices and price increases do not continue their current upward trajectory, driving prices further from reasonable alignment with the added benefits for patients.
- Payers, PBMs and plan sponsors should increase transparency around the role of discounting and rebate practice in formulary design for all interventions, including biosimilars.
- Policymakers should continue work on alternatives to the current rebate system that will allow the market to reward the competitive advantages of lower-priced, equally effective biosimilar treatment options.

## Clinical Analyses

How strong is the evidence that JAK inhibitors improve outcomes in patients with moderately-to-severely active rheumatoid arthritis with conventional DMARDs compared to:

- conventional DMARDs alone or,
- adalimumab with cDMARDs

### TIM-NAÏVE POPULATION

Intervention	Comparator	Rating
Upadacitinib	cDMARDs	High certainty of a substantial net health benefit
Tofacitinib	cDMARDs	High certainty of a substantial net health benefit
Baricitinib	cDMARDs	Insufficient level of certainty
Upadacitinib	Adalimumab	Moderate certainty of a small or substantial net health benefit with a high certainty of at least a small net health benefit
Tofacitinib	Adalimumab	High certainty of a comparable net health benefit
Baricitinib	Adalimumab	Insufficient level of certainty

### TIM-EXPERIENCED POPULATION

Intervention	Comparator	Rating
Upadacitinib	cDMARDs	Moderate certainty of a small or substantial net health benefit with a high certainty of at least a small net health benefit
Tofacitinib	cDMARDs	Moderate certainty of a small or substantial net health benefit with a high certainty of at least a small net health benefit
Baricitinib	cDMARDs	Moderate certainty of a small or substantial net health benefit with a high certainty of at least a small net health benefit

## Clinical Analyses (continued)

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**Biosimilar rating:** PLANETRA was a large study with relatively long follow up. The study found no clinically important or statistically significant differences in benefits or harms between infliximab-dyyb and its reference product infliximab at weeks 30, 54, and 102. Observational data also support no important differences between the two therapies. Using the ICER Evidence Matrix, the biosimilar infliximab-dyyb has high certainty of comparable net health benefit (“C”) relative to its reference product.

### KEY CLINICAL BENEFITS AND HARMS STUDIED IN CLINICAL TRIALS

These results summarize key findings from ICER’s report, and do not reflect all comparisons between agents reflected in the report. For more information, see ICER’s full report.

#### **ICER’s review analyzed the drugs’ performance on several key outcomes:**

**American College of Rheumatology (ACR) Criteria:** A measure of the level of improvement in the number of tender or swollen joints along with improvement in three of five criteria related to patient and physician assessment, pain, and disability.

**Health Assessment Questionnaire for Rheumatoid Arthritis Disability Index (HAQ-DI):** A questionnaire that uses patient-reported outcomes to assesses the level of disease-related disability and functional impairment a patient is experiencing

**Low Disease Activity or Remission:** Substantial reductions in tender/swollen joints, pain, disability, and/or laboratory indices as measured on multiple scales.

## Clinical Analyses (continued)

### BIOLOGIC NAÏVE (TIM NAÏVE) PATIENTS

#### Compared to cDMARD

	Low-Disease Activity/ Remission		ACR Response		HAQ-DI	
	3 months	6 months	3 months	6 months	3 months	6 months
Timepoint	3 months	6 months	3 months	6 months	3 months	6 months
<b>Upadacitinib</b>	Superior	Superior	Superior	Superior	Superior	Superior
<b>Tofacitinib</b>	Comparable	Comparable	Superior	Comparable	Superior	Superior
<b>Baricitinib</b>	Not Reviewed	Not Reviewed	Not Reviewed	Not Reviewed	Not Reviewed	Not Reviewed

#### Compared to adalimumab

	Low-Disease Activity/ Remission		ACR Response		HAQ-DI	
	3 months	6 months	3 months	6 months	3 months	6 months
Timepoint	3 months	6 months	3 months	6 months	3 months	6 months
<b>Upadacitinib</b>	Superior	Superior	Superior	Superior	Superior	Superior
<b>Tofacitinib</b>	Comparable	Comparable	Comparable	Comparable	Comparable	Comparable
<b>Baricitinib</b>	Not Reviewed	Not Reviewed	Not Reviewed	Not Reviewed	Not Reviewed	Not Reviewed

## Clinical Analyses (continued)

### BIOLOGIC EXPERIENCED (TIM-EXPERIENCED) PATIENTS

#### Combination with cDMARD

Timepoint	Low-Disease Activity/ Remission		ACR Response		HAQ-DI	
	3 months	6 months	3 months	6 months	3 months	6 months
<b>Upadacitinib</b>	Superior	Comparable	Superior	Comparable	No Data	No Data
<b>Tofacitinib</b>	Comparable	No Data	Superior	No Data	Comparable	No Data
<b>Baricitinib</b>	Comparable	Comparable	Superior	Superior	Not Reviewed	Comparable

### HARMS

**Black-Box Warnings:** All three JAK inhibitors carry black-box warnings for serious infections, lymphoma, testing for latent tuberculosis prior to initiating therapy, monitoring for active tuberculosis and thrombosis.

**Within 6-months Rates:** of short-term serious adverse events were generally comparable across all treatments, including JAK inhibitors, adalimumab, and conventional DMARDs. Infections (e.g., upper respiratory tract infections, bronchitis, nasopharyngitis) were the most common adverse events during treatment.

**1 or more years:** Based on long-term trial data, upadacitinib, tofacitinib, and baricitinib showed comparable overall safety profiles.

## Clinical Analyses (continued)

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### SOURCES OF UNCERTAINTY

**Comparison between JAK inhibitors:** More robust data are needed to determine how the JAK inhibitors compare to each other.

**Outcome Timepoints:** Clinical trials do not consistently report 3-month outcomes, which is when treatment-switch decisions are increasingly occurring.

**Unanswered Questions:** Many aspects of the management of RA are not well understood, including the relationship between levels of disease activity and radiographic evidence of joint damage and whether there are clinical factors that predict response to specific therapies.

**Tools to Capture Patient Experience:** The totality of the disease's impact on patients, families, and caregivers are not adequately captured by current tools; new instruments to measure the patient experience are needed.

## Economic Analyses

### LONG-TERM COST-EFFECTIVENESS

#### Do these treatments meet established thresholds for long-term cost-effectiveness?

The incremental cost-effectiveness ratio for upadacitinib versus adalimumab falls within commonly cited thresholds for cost-effectiveness. However, ICER’s [2017 review of treatments for rheumatoid arthritis](#) found that adalimumab itself may be priced above commonly cited cost-effectiveness thresholds.

Results from the modeling comparison of tofacitinib to conventional DMARDs suggest that tofacitinib provides similar QALY gains at one year, at a higher cost. Adalimumab also resulted in similar QALY gains as cDMARDs after one year of treatment at a higher cost.

### VALUE-BASED PRICING AND BUDGET IMPACT

#### What is a fair price for upadacitinib based on its value to patients and the health care system?

	Upadacitinib
Annual WAC	\$59,860
Annual Price to Achieve \$100,000/QALY Threshold	\$44,144
Annual Price to Achieve \$150,000/QALY Threshold	\$44,822
Change from WAC Required to Reach Threshold Prices	-25% to -26%
Net price within range?	Yes

The value-based price benchmark range for upadacitinib represents a 25-26% discount off of upadacitinib’s annual list price of \$59,860. This suggested discount is consistent with the rebates ICER assumes the manufacturer is currently offering.

Because upadacitinib does not appear to lengthen patients’ lives when compared to adalimumab, ICER did not calculate what price would be needed to reach alternative thresholds based on Equal Value of Life Years Gained (evLYG).

Due to insufficient head-to-head evidence against adalimumab, ICER did not calculate value-based price benchmarks for either tofacitinib or baricitinib.

## Economic Analyses (continued)

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### POTENTIAL SHORT-TERM BUDGET IMPACT

#### How many patients can be treated before crossing ICER's \$819 million budget impact threshold?

At its current price of \$59,860, the annual potential budget impact of treating the entire eligible population across all prices did not exceed the \$819 million threshold.

## Voting Results

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The California CEPAC deliberated on key questions raised by ICER's report at a public meeting on December 9th, 2019. The results of the votes are presented below. More detail on the voting results is provided in the [full report](#).

### CLINICAL EVIDENCE

#### TIM Naïve

- All panelists found that evidence is adequate to demonstrate that the net health benefit of upadacitinib plus a cDMARD is superior to that provided by a cDMARD alone.
- A majority of panelists found the evidence is adequate to demonstrate that the net health benefit of upadacitinib plus cDMARD is superior to that provided by adalimumab plus a cDMARD.
- All panelists found that evidence is adequate to demonstrate that the net health benefit of tofacitinib plus cDMARD is superior to that provided by a cDMARD alone.
- The panel did not find adequate evidence to demonstrate that the net health benefit of tofacitinib plus cDMARD is superior to that provided by adalimumab plus cDMARD.
- The panel did not find adequate evidence to distinguish the net health benefit between upadacitinib and tofacitinib.
- A majority of panelists found that infliximab-dyyb produces a net health benefit comparable to that of the originator biologic infliximab (Remicade™).

## Voting Results (continued)

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### TIM Experienced

- All panelists found that evidence is adequate to demonstrate that the net health benefit of upadacitinib plus a cDMARD is superior to that provided by a cDMARD alone.
- All panelists found the evidence is adequate to demonstrate that the net health benefit of tofacitinib plus cDMARD is superior to that provided by cDMARD alone.
- All panelists found that evidence is adequate to demonstrate that the net health benefit of baricitinib plus cDMARD is superior to that provided by a cDMARD alone.

### Biosimilars

- All panelists found that evidence is adequate to demonstrate that the net health benefit of the biosimilar infliximab-dyyb clinically equivalent to its reference biologic Remicade.

### OTHER BENEFITS AND CONTEXTUAL CONSIDERATIONS

- A majority of panelists found that upadacitinib plus cDMARD will significantly improve patient outcomes in comparison to adalimumab plus cDMARD.
- A majority of panelists found that upadacitinib is intended for the care of individuals with a condition of particularity high severity.

### LONG-TERM VALUE FOR MONEY

- A majority of panelists found that upadacitinib plus cDMARD is deemed to be low long-term value for money at currently estimated net pricing compared to adalimumab plus cDMARD.

## Policy Recommendations

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### For Payers

- Health plan sponsors, insurers, PBMs, and provider groups should work together to promote greater use of biosimilars by implementing switching programs that provide broad support to patients while assuring that patients who do not respond well to biosimilars are able to access reference products and/or obtain other targeted treatment options without delay.
- Payers, PBMs and plan sponsors should increase transparency around the role of discounting and rebate practice in formulary design.

### For Providers

- The FDA should require that randomized trials of new therapies always include an active comparator.

### For Manufacturers and Clinical Societies

- Clinical societies and manufacturers should establish standardized assessments to allow for rigorous direct and indirect comparisons of evidence across studies and therapeutic alternatives.
- Researchers should separate outcomes that measure inflammation from those that measure pain.
- Clinical societies should educate their clinician members that the evidence behind biosimilars is sound and that whenever they are available at a lower cost than reference products, they should be the preferred option given the benefits of lower costs for patients and the health care system.

### For Patient Advocacy Groups

- Patient groups should educate their members that biosimilars are as safe and effective as reference products and that starting on a biosimilar, or switching to one, is clinically responsible and may be financially beneficial.

## About ICER

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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)).