

NOTICE: On April 14, 2017 the FDA issued a complete response letter for baricitinib indicating that the FDA is unable to approve the application in its current form and requires additional data to determine the most appropriate doses and to further characterize safety concerns across treatment arms.

For Rheumatoid Arthritis

Do these new drugs meet an important need?

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.**

RA is more common in women and may occur at any age, with peak incidence occurring at ages 50-60 years. Symptoms of RA include morning stiffness, joint swelling, most commonly in the feet, hands, and knees. If not well-controlled, it can lead to permanent joint damage and deformity.

Treating rheumatoid arthritis

There are two key types of medications used in RA treatment: **conventional disease-modifying anti-rheumatic drugs (DMARDs)** and a newer group of drugs known as **targeted immune modulators (TIMs)**. Methotrexate is the most widely used conventional DMARD because of its effectiveness and relative tolerability. However, only about 50% of patients treated with methotrexate alone see sufficient improvement in their condition.

Over the past two decades, the introduction of TIMs has changed the course of the disease for many RA patients. Historically, RA was associated with both progressive disability and a shortened lifespan, but improvements in survival and other key outcomes have been observed in the TIM era.

Drugs under review

While TIMs have been highly effective in improving outcomes in comparison to conventional DMARDs, there is uncertainty around the comparative effectiveness of the different types of TIMs and the most effective sequence of TIM therapy. This review focuses on the comparative clinical effectiveness and value of TIMs currently used in RA treatment, as well as TIMs currently under review by the Food and Drug Administration (FDA).

Class	Intervention	Unit	Unit WAC*	Unit Net Price**	Annual Drug Cost***
TNFα inhibitor	Adalimumab (Humira®, AbbVie)	40mg, subcutaneous	\$2,221	\$1,554	\$40,415
	Certolizumab pegol (Cimzia®, UCB)	200mg, subcutaneous	\$1840	\$1,288	\$34,775
	Etanercept (Enbrel®, Amgen)	50mg, subcutaneous	\$1,111	\$777	\$40,422
	Golimumab (Simponi®, Janssen)	50mg, subcutaneous	\$4,150	\$2,905	\$34,863
	Golimumab (Simponi Aria®, Janssen)	50mg, intravenous	\$1,592	\$1,114	\$29,719
	Infliximab (Remicade®, Janssen Biotech)	100mg, intravenous	\$1,168	\$817	\$28,906
T-cell inhibitor	Abatacept (Orencia®, Bristol Myers-Squibb)	250mg, intravenous	\$987	\$691	\$27,637
	Abatacept (Orencia®, Bristol Myers-Squibb)	125mg, subcutaneous	\$957	\$814	\$42,306
CD20-directed cytolytic B-cell antibody	Rituximab (Rituxan®, Genentech/Biogen)	100mg, intravenous	\$835	\$710	\$30,764
IL-6 inhibitor	Sarilumab (Kevzara™, Sanofi/Regeneron)	Pending FDA approval			
	Tocilizumab (Actemra®, Genentech)	20mg, intravenous	\$95	\$76	\$27,627
	Tocilizumab (Actemra®, Genentech)	162mg, subcutaneous	\$898	\$719	\$21,861
JAK inhibitor	Baricitinib (Olumiant™, Eli Lilly)	Pending FDA Approval			
	Tofacitinib (Xeljanz®, Pfizer)	5mg, oral	\$63	\$60	\$43,873

* Price reflects the wholesale acquisition price listed on Red Book Online (Greenwood Village, CO: Truven Health Analytics. <http://www.micromedexsolutions.com/>. Accessed February 2017)

** 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

*** Based on discounted WAC per unit. Includes the cost of drug therapy, and does not include any costs associated with administration or monitoring. Average over three years of treatment assuming 100% compliance.

How strong is the evidence that TIMs improve patient outcomes?

Drug performance

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:

- **Low Disease Activity or Remission:** Substantial reductions in tender/swollen joints, pain, disability, and/or laboratory indices as measured on multiple scales.
- **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.
- **Radiographic Progression:** Changes in the level of joint erosion, narrowing between spaces, and destruction as observed on X-ray.

TIMs Compared to Conventional DMARDs

All 11 TIMs evaluated in combination with conventional DMARDs significantly improved outcomes in disease activity, remission, and ACR response compared to conventional DMARDs alone. Radiographic progression was also significantly reduced with most TIMs in comparison to conventional DMARDs, but differences in the progression measures used made comparisons across studies difficult. Improvements in function and disability as measured on the HAQ-DI were statistically superior for all TIMs compared to conventional DMARDs. Findings were much more limited for TIM monotherapy.

Head-to-Head TIM Trials

TIMs were most commonly compared to adalimumab in head-to-head trials. The tables below outline the results of trials assessing sarilumab and tocilizumab as monotherapy, as well as several TIMs used in combination therapy with conventional DMARDs compared to adalimumab combination therapy.

Monotherapy (versus adalimumab)

	Low Disease Activity/ Remission	ACR Response	Radiographic Progression	HAQ-DI
Sarilumab	↑	↑	No data	↑
Tocilizumab	↑	↑	No data	↔

Combination Therapy (versus adalimumab)

	Low Disease Activity/ Remission	ACR Response	Radiographic Progression	HAQ-DI
Abatacept (SC)	↔	↔	↔	↔
Tofacitinib	↔	↔	No data	↔
Baricitinib	↑	↑	↔	↑
Certolizumab Pegol	↔	↔	No data	↔
Etanercept	↔	No data	No data	No data

Superior ↑
Comparable ↔
Inferior ↓
No Data Identified No data

How strong is the evidence that TIMs improve patient outcomes? (continued)

Sources of Uncertainty

Few Head-to-Head Studies Among TIMs: There are few published studies evaluating head-to-head comparisons among TIMs. Instead, most studies evaluate TIM therapy in comparison with conventional DMARDs in patients who have already had an inadequate response to conventional DMARD therapy. A more relevant comparator in this population would be another TIM.

Treatment Reassignments: Treatment reassignments in trials may not reflect therapeutic switching in real world practice.

Measurement Instruments: The use of instruments (e.g., to measure disease activity and progression) have changed over time and are not measured consistently.

Payer Requirements: In the US, most private payers require use of a TNF α inhibitor as initial TIM therapy, and many give etanercept and adalimumab preferred status. Evidence on sequencing and the effectiveness of switches between versus within classes is still emerging.

Long-term Effects: TIM therapies are chronic, and the long-term effects of prolonged immunomodulation—both clinical benefits and potential harms—are not well-understood for all therapies.

Patient-reported Outcomes: Patient groups noted that the current tools for assessing patient-reported outcomes do not sufficiently capture their experience, but to date no new instruments have been accepted into common use in clinical studies.

ICER's Evidence Rating

We have high certainty that all FDA-approved TIMs provide a substantial net health benefit relative to conventional DMARD therapy alone. Although the long-term effectiveness and safety of the two investigational TIMs (baricitinib and sarilumab) is less clear, we have moderate certainty of an incremental or better net health benefit with these two agents compared to conventional DMARDs.

Head-to-head comparisons of TIMs:

- Among monotherapy regimens, there is moderate certainty of an incremental or better net health benefit for sarilumab and intravenous tocilizumab compared to adalimumab.
- Combination (i.e., with conventional DMARDs) regimens involving tofacitinib, subcutaneous abatacept, certolizumab pegol, and etanercept have been compared to adalimumab + methotrexate in single trials. Comparisons yielded comparable net health benefits. In a single trial, combination therapy with baricitinib provided statistically-significant but modest benefits over adalimumab, yielding a “comparable or better” rating.
- For TIMs that have never been compared head to head in a randomized setting, we judge there to be insufficient evidence to differentiate among therapies, including intra-class comparisons of the remaining TNF α inhibitors, IL-6 inhibitors, and JAK inhibitors.

ICER's complete evidence ratings are available in the [full report](#).

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

Long-term cost-effectiveness at current net prices

TNF α

Adalimumab:	\$232,644/QALY
Certolizumab pegol:	\$209,736/QALY
Etanercept:	\$212,021/QALY
Golimumab SC:	\$222,380/QALY
Golimumab IV:	\$204,212/QALY
Infliximab:	\$202,824/QALY

T-cell inhibitor

Abatacept IV:	\$191,317/QALY
Abatacept SC:	\$225,853/QALY

CD20-directed cytolytic B-cell antibody

Rituximab:	\$198,056/QALY
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IL-6 inhibitor

Tocilizumab IV:	\$183,949/QALY
Tocilizumab SC:	\$168,660/QALY

JAK inhibitor

Tofacitinib:	\$271,749/QALY
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ICER calculated the incremental cost-effectiveness ratio for each of the TIMs (in combination with conventional DMARD and as monotherapy) compared to conventional DMARD therapy alone and to the TIM market leader, adalimumab. 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 \$50,000-\$150,000. Drug costs were based on estimated net prices that account for discounts and rebates across payer types, so further discounts would be required to reach these cost-effectiveness thresholds.

When compared to market leader adalimumab, eight TIMs were less costly and more effective, two other TIMs (abatacept administered subcutaneously and etanercept) were more costly but also more effective, and one TIM (tofacitinib) was more costly and less effective.

When comparing monotherapy regimens, tocilizumab monotherapy was less costly and more effective than adalimumab monotherapy, while etanercept was more costly and more effective than adalimumab.

Potential short-term budget impact at net price

Potential short-term budget impact at net price was evaluated only for the two new treatments for moderate-to-severe RA patients: sarilumab (including monotherapy) and baricitinib, both of which are currently pending FDA approval.

If priced in a way that would achieve established cost-effectiveness thresholds of \$50,000, \$100,000 and \$150,000 per QALY, both sarilumab and baricitinib would

result in cost savings. Priced in this way, neither drug poses a threat to health system affordability in the short term (five years), as neither of these therapies exceeded ICER’s potential budget impact threshold of \$915 million annually. \$915 million is 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 targeted immune modulators based on their value to patients and the health care system? (continued)

ICER's Value-Based Price Benchmark

Class	Intervention	WAC per unit	Value-based unit price	Discount from WAC to reach thresholds	Average net price within benchmark range?
TNF α inhibitor	Adalimumab (40mg)	\$2,221	\$699.49-\$1,010.38	55% to 69%	X
	Certolizumab pegol (200mg)	\$1,840	\$643.98-\$927.33	50% to 65%	X
	Etanercept (50mg)	\$1,111	\$380.90-\$559.69	50% to 66%	X
	Golimumab SC (50mg)	\$4,150	\$1,365.48-\$1,975.58	52% to 67%	X
	Golimumab IV (50mg)	\$1,592	\$557.23-\$824.70	48% to 65%	X
	Infliximab (100mg)	\$1,168	\$416.91-\$604.93	48% to 64%	X
T-cell inhibitor	Abatacept IV (250mg)	\$987	\$366.19-\$538.92	45% to 63%	X
	Abatacept SC (125mg)	\$957	\$374.24-\$545.09	43% to 61%	X
CD20-directed cytolytic B-cell antibody	Rituximab (100mg)	\$835	\$369.17-\$539.55	35% to 56%	X
IL-6 inhibitor	Sarilumab	–	\$445.56-\$646.78	–	–
	Tocilizumab IV 20mg	\$95	\$41.74-\$61.48	35% to 56%	X
	Tocilizumab SC (162mg)	\$898	\$438.38-\$639.60	29% to 51%	X
JAK inhibitor	Baricitinib	–	\$24.64 - \$36.06	–	–
	Tofacitinib (5mg)	\$63	\$23.44-\$34.26	46% to 63%	X

To fall within ICER's threshold value range of \$100,000 to \$150,000 per QALY, all TIMs would require discounts that are greater than the current discounts from WAC.

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

California Technology Assessment Forum Votes

The New England Comparative Effectiveness Public Advisory Council deliberated on key questions raised by ICER's report at a public meeting on March 24, 2017. The results of the votes are presented below. More detail on the voting results is provided in the [full report](#).

Comparative Effectiveness of TIMs as Monotherapy:

1. Is the evidence adequate to demonstrate that the net health benefit of tocilizumab monotherapy is superior to that provided by adalimumab monotherapy?

Yes: 11 votes	No: 0 votes
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2. Is the evidence adequate to demonstrate that the net health benefit of sarilumab monotherapy is superior to that provided by adalimumab monotherapy?

Yes: 11 votes	No: 0 votes
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3. Is the evidence adequate to distinguish the net health benefit between tocilizumab monotherapy and sarilumab monotherapy?

Yes: 0 votes	No: 11 votes
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4. Is the evidence adequate to demonstrate that the net health benefit of tofacitinib monotherapy is superior to that provided by adalimumab monotherapy?

Yes: 0 votes	No: 11 votes
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5. Is the evidence adequate to demonstrate that the net health benefit of baricitinib monotherapy is superior to that provided by adalimumab monotherapy?

Yes: 0 votes	No: 11 votes
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6. Is the evidence adequate to distinguish the net health benefit between tofacitinib monotherapy and baricitinib monotherapy?

Yes: 0 votes	No: 11 votes
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Comparative Effectiveness of TIMs in Combination with conventional DMARDs:

7. Is the evidence adequate to demonstrate that the net health benefit of tocilizumab + cDMARD therapy is superior to that provided by adalimumab + cDMARD therapy?

Yes: 1 vote	No: 10 votes
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8. Is the evidence adequate to demonstrate that the net health benefit of sarilumab + cDMARD therapy is superior to that provided by adalimumab + cDMARD therapy?

Yes: 0 votes	No: 11 votes
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9. Is the evidence adequate to distinguish the net health benefit between tocilizumab + cDMARD therapy and sarilumab + cDMARD therapy?

Yes: 0 votes	No: 11 votes
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10. Is the evidence adequate to demonstrate that the net health benefit of tofacitinib + cDMARD therapy is superior to that provided by adalimumab + cDMARD therapy?

Yes: 0 votes	No: 11 votes
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11. Is the evidence adequate to demonstrate that the net health benefit of baricitinib + cDMARD therapy is superior to that provided by adalimumab + cDMARD therapy?

Yes: 6 votes	No: 5 votes
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12. Is the evidence adequate to distinguish the net health benefit between tofacitinib + cDMARD therapy and baricitinib + cDMARD therapy?

Yes: 0 votes	No: 11 votes
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Comparative Value of TIMs:

13. Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money for tocilizumab monotherapy in comparison to adalimumab monotherapy?

Low: 0 votes	Intermediate: 4 votes	High: 7 votes
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Remaining votes on value not taken due to clinical effectiveness votes finding insufficient evidence to show net health benefit.

Key Policy Implications and Recommendations

The New England CEPAC engaged in a moderated discussion with a policy roundtable of subject-matter experts about how best to apply evidence on targeted immunomodulators for plaque psoriasis in policy and practice. The roundtable included a patient and patient advocate, clinical experts, drug manufacturer representatives, and public and private payer representatives. Many of the roundtable themes focused on price negotiations which are based on manufacturer rebates and concessions and drive coverage policies for payers.

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](#).

Payers and Pharmacy Benefit Managers

- Consider including in prior authorization processes the requirement that conventional DMARD therapy dosing be optimized before initiating TIM therapy.
- If step therapy protocols require patients to fail one or two TNF α inhibitors before switching to another TIM, develop a quick and transparent exception process for specific situations.
- Payers should reach out to providers to learn from their experience with prior authorization in order to streamline and improve the process.
- Allow patients who are stable on effective treatment to remain on therapy when they change insurers.
- Reconsider step therapy if pricing becomes better aligned with clinical value.
- Negotiate better rebates and share savings with patients.
- Increase transparency around the role of discounting and rebate practice in formulary design.
- Design innovative risk-sharing payment agreements, including pay-for-performance contracts, value-based contracting, and indication-specific pricing.

Providers, Clinical Societies, and Payers

- Develop clinical guidelines and coverage policies that closely align with the evidence on outcomes of patients stratified by prognostic factors, allowing for earlier use of TIM therapy in patients with poor prognostic factors.

Clinical Societies and Manufacturers

- Establish standardized assessments to allow for rigorous direct and indirect comparisons of evidence across studies and therapeutic alternatives.

Public Policy Decision Makers

- Policy makers may need to consider regulatory intervention to ensure that drug prices do not continue to increase, moving further from reasonable alignment with the added benefits to patients.

Conclusion

Comparative Clinical Effectiveness

- TIMs substantially improve health outcomes compared to conventional DMARDs. Evidence to distinguish the effectiveness among different TIMs is limited; however, sarilumab and tocilizumab (intravenous) monotherapy seem to be superior to adalimumab, and combination regimens involving baricitinib, tofacitinib, abatacept (subcutaneous), certolizumab pegol, and etanercept appear to provide comparable net health benefits in comparison to adalimumab.

Comparative Value

- The additional cost of TIMs led to estimates that were well above commonly cited thresholds for cost-effectiveness, and the discounts required to achieve these thresholds are greater than estimated current discounts from WAC. Compared to the market leader adalimumab, most TIMs in combination with conventional DMARDs were more favorable (i.e., had lower costs and higher QALYs).

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).