

INFLIXIMAB (REMICADE®, INFLECTRA™, RENFLEXIS™)

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Related Policies
<ul style="list-style-type: none"> • Acquired Rare Disease Drug Therapy Exception Process • Experimental/Investigational Treatment • Experimental/Investigational Treatment for NJ Plans • Maximum Dosage • Specialty Medication Administration – Site of Care Review Guidelines • Specialty Pharmacy for Certain Specialty Medications Administered in an Outpatient Hospital Setting

INSTRUCTIONS FOR USE

This Clinical Policy provides assistance in interpreting Oxford benefit plans. Unless otherwise stated, Oxford policies do not apply to Medicare Advantage members. Oxford reserves the right, in its sole discretion, to modify its policies as necessary. This Clinical Policy is provided for informational purposes. It does not constitute medical advice. The term Oxford includes Oxford Health Plans, LLC and all of its subsidiaries as appropriate for these policies.

When deciding coverage, the member specific benefit plan document must be referenced. The terms of the member specific benefit plan document [e.g., Certificate of Coverage (COC), Schedule of Benefits (SOB), and/or Summary Plan Description (SPD)] may differ greatly from the standard benefit plan upon which this Clinical Policy is based. In the event of a conflict, the member specific benefit plan document supersedes this Clinical Policy. All reviewers must first identify member eligibility, any federal or state regulatory requirements, and the member specific benefit plan coverage prior to use of this Clinical Policy. Other Policies may apply.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

CONDITIONS OF COVERAGE

Applicable Lines of Business/Products	This policy applies to Oxford Commercial plan membership.
Benefit Type	General benefits package
Referral Required (Does not apply to non-gatekeeper products)	Yes - Office No - Outpatient, Home
Authorization Required (Precertification always required for inpatient admission)	Yes - Outpatient, Home ^{1,2,3} Yes - Office ^{1,2}
Precertification with Medical Director Review Required	Yes ^{1,2,3}
Applicable Site(s) of Service (If site of service is not listed, Medical Director review is required)	Office, Outpatient ^{3,4} , Home
Special Considerations	¹ Precertification with review by a Medical Director or their designee is required for Remicade in the home or outpatient setting. No precertification is required for Remicade administered in the office setting. ² Precertification with review by a Medical Director or their designee is required for Inflectra and Renflexis in all

Special Considerations (continued)

settings/sites of service.

³Additional precertification requirements apply to requests for hospital outpatient facility infusion of Inflectra, Remicade, and Renflexis; refer to the policy titled [Specialty Medication Administration - Site of Care Review Guidelines](#).

⁴Participating hospitals are required to purchase Inflectra™ (infliximab-dyyb), Remicade® (infliximab), and Renflexis™ (infliximab-abda) from the BriovaRx Specialty Pharmacy when the medication is administered in an outpatient hospital setting; refer to the policy titled [Specialty Pharmacy for Certain Specialty Medications Administered in an Outpatient Hospital Setting](#) for additional information.

BENEFIT CONSIDERATIONS

Before using this policy, please check the member specific benefit plan document and any federal or state mandates, if applicable.

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The member specific benefit document must be consulted to make coverage decisions for this service. Refer to: [Experimental/Investigational Treatment](#) and [Experimental/Investigational Treatment for NJ Plans](#).

Some states mandate benefit coverage for off-label use of drugs under some circumstances. Consult regulations for your individual state to determine whether and under what circumstances such coverage is mandated for a particular state. Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. Refer to: [Acquired Rare Disease Drug Therapy Exception Process](#).

Essential Health Benefits for Individual and Small Group

For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group plans (inside and outside of Exchanges) to provide coverage for ten categories of Essential Health Benefits ("EHBs"). Large group plans (both self-funded and fully insured), and small group ASO plans, are not subject to the requirement to offer coverage for EHBs. However, if such plans choose to provide coverage for benefits which are deemed EHBs, the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans. The determination of which benefits constitute EHBs is made on a state by state basis. As such, when using this policy, it is important to refer to the member specific benefit plan document to determine benefit coverage.

COVERAGE RATIONALE

This policy refers to the following infliximab products:

- Inflectra™ (infliximab-dyyb)
- Remicade® (infliximab)
- Renflexis™ (infliximab-abda)

Preferred Product

Remicade® (infliximab) is the preferred infliximab product. Coverage will be provided for Remicade® contingent on the coverage criteria in the *Diagnosis-Specific Criteria* section.

Coverage for Inflectra™ (infliximab-dyyb) or Renflexis™ (infliximab-abda) will be provided contingent on the criteria in this section and the coverage criteria in the *Diagnosis-Specific Criteria* section. In order to continue coverage, members already on Inflectra™ or Renflexis™ will be required to change therapy to Remicade® unless they meet the criteria in this section.

Preferred Product Criteria

Treatment with Inflectra™ (infliximab-dyyb), Renflexis™ (infliximab-abda) or other infliximab biosimilar is medically necessary for the indications specified in this policy when the following criteria are met:

- **Both** of the following:
 - **One** of the following:
 - **Both** of the following:

- History of a trial of at least 14 weeks of Remicade resulting in minimal clinical response to therapy and residual disease activity.
- Physician attests that in their clinical opinion the clinical response would be expected to be superior with Inflectra or other infliximab biosimilar product, than experienced with Remicade.

or

- **Both** of the following:

- History of intolerance or adverse event to Remicade.
- Physician attests that in their clinical opinion the same intolerance or adverse event would not be expected to occur with Inflectra or other infliximab biosimilar product.

and

- **Both** of the following:

- Patient has **NOT** had a loss of a favorable response after established maintenance therapy with Remicade or other infliximab product.
- Patient has **NOT** developed neutralizing antibodies to any infliximab product that has led to an attenuation of efficacy of therapy.⁶¹

Diagnosis-Specific Criteria

"Infliximab" will be used to refer to all infliximab products.

Infliximab is proven and medically necessary for the treatment of:

- **Ankylosing spondylitis** when the following criterion is met: ^{1,57,62}
 - Diagnosis of ankylosing spondylitis (AS).
- **Crohn's disease** when the following criterion is met:^{1,3-5,41, 57,62}
 - **One** of the following:¹
 - Diagnosis of fistulizing Crohn's disease (Crohn's Disease Activity Index (CDAI) ≥ 220 and ≤ 400); **or**
 - **Both** of the following:
 - Diagnosis of moderately to severely active Crohn's disease; and
 - History of failure, contraindication, or intolerance to at least **one** conventional therapy (e.g., corticosteroids, 6-mercaptopurine, azathioprine, methotrexate, etc.).
- **Noninfectious uveitis** when BOTH of the following criteria are met:^{12-14,15,17}
 - Diagnosis of refractory noninfectious uveitis that is causing or threatening vision loss (e.g., noninfectious uveitis associated with Behçet's or Reiter's syndromes); **and**
 - History of failure, contraindication, or intolerance to **ALL** of the following:
 - Topical corticosteroids;
 - Systemic corticosteroids;
 - Immunosuppressive drugs (e.g., azathioprine, cyclosporine, or methotrexate).
- **Plaque psoriasis** when BOTH of the following criteria are met:^{1,57,62}
 - Diagnosis of chronic severe plaque psoriasis i.e., extensive and/or disabling); **and**
 - Patient is a candidate for systemic therapy.
- **Psoriatic arthritis** when the following criterion is met:^{1,57,62}
 - Diagnosis of psoriatic arthritis (PsA).
- **Rheumatoid arthritis** when BOTH of the following criteria are met:^{1,57,62}
 - Diagnosis of moderately to severely active rheumatoid arthritis (RA); **and**
 - **One** of the following:
 - Member is receiving concurrent therapy with methotrexate;
 - History of contraindication or intolerance to methotrexate.
- **Sarcoidosis** when ALL of the following criteria are met:^{6, 25, 39-40, 46, 52}
 - Diagnosis of sarcoidosis; **and**
 - History of failure, contraindication, or intolerance to corticosteroids (e.g., prednisone, methylprednisolone); **and**
 - History of failure, contraindication, or intolerance to **one** immunosuppressant (e.g., methotrexate, cyclophosphamide, azathioprine).
- **Ulcerative colitis** when BOTH of the following criteria are met:^{1,57,62}
 - Diagnosis of moderately to severely active ulcerative colitis (UC); **and**
 - History of failure, contraindication, or intolerance to at least **one** conventional therapy e.g., 6-mercaptopurine, aminosalicilate, azathioprine, corticosteroids.

There may be other conditions that qualify as serious, rare diseases for which the use of infliximab may be appropriate. Please refer to the [Benefit Considerations](#) section of this policy for additional information.

Infliximab is unproven and not medically necessary in the treatment of:

- Still's disease
- Sjogren's syndrome

- Graft-vs-host disease
- Myelodysplastic syndromes
- Undifferentiated spondyloarthropathy
- Reiter's syndrome
- Hidradenitis suppurativa
- Wegener's granulomatosis
- Juvenile idiopathic arthritis (juvenile rheumatoid arthritis)

Infliximab is unproven and not medically necessary for the treatment of the above conditions because statistically robust randomized controlled trials are needed to address the issue of whether Infliximab has sufficient superiority in clinical efficacy compared to other available treatments to justify the inherent clinical risk in the use of a monoclonal antibody anti-tumor necrosis factor agent.

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Remicade is a tumor necrosis factor (TNF) blocker indicated for:¹

- Crohn's disease:
 - Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy.
 - Reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing disease.
- Pediatric Crohn's disease:
 - Reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active disease who have had an inadequate response to conventional therapy.
- Ulcerative colitis:
 - Reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in patients with moderately to severely active disease who have had an inadequate response to conventional therapy.
- Pediatric ulcerative colitis:
 - Reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active disease who have had an inadequate response to conventional therapy.
- Rheumatoid arthritis in combination with methotrexate:
 - Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active disease.
- Plaque psoriasis:
 - Treatment of adult patients with chronic severe (i.e., extensive and /or disabling) plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate.
- Psoriatic arthritis:
 - Reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in patients with psoriatic arthritis.
- Ankylosing spondylitis:
 - Reducing signs and symptoms in patients with active disease.

Inflectra (infliximab-dyyb) and Renflexis (infliximab-abda) are biosimilar* to Remicade (infliximab). Inflectra and Renflexis are tumor necrosis factor (TNF) blockers indicated for:⁵⁷⁻⁶⁰

- Crohn's disease:
 - Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy.
 - Reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing disease.
- Pediatric Crohn's disease:
 - Reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active disease who have had an inadequate response to conventional therapy.
- Ulcerative colitis:
 - Reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in patients with moderately to severely active disease who have had an inadequate response to conventional therapy.
- Rheumatoid arthritis in combination with methotrexate:
 - Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active disease.

- Ankylosing spondylitis:
 - Reducing signs and symptoms in patients with active disease.
- Psoriatic arthritis:
 - Reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in patients with psoriatic arthritis.
- Plaque psoriasis:
 - Treatment of adult patients with chronic severe (i.e., extensive and /or disabling) plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate.

*Biosimilar means that the biological product is approved based on data demonstrating that it is highly similar to an FDA-approved biological product, known as a reference product, and that there are no clinically meaningful differences between the biosimilar product and the reference product.

The FDA issued an alert dated September 7, 2011, to inform healthcare professionals that the Boxed Warning for the entire class of Tumor Necrosis Factor-alpha (TNFα) blockers has been updated to include the risk of infection from two bacterial pathogens, *Legionella* and *Listeria*. In addition, the Boxed Warning and Warnings and Precautions sections of the labels for all of the TNFα blockers have been revised so that they contain consistent information about the risk for serious infections and the associated disease-causing pathogens.¹¹

The FDA issued an update on November 3, 2011 regarding their ongoing safety review of Tumor Necrosis Factor (TNF) blockers and malignancy in children, adolescents, and young adults (30 years of age or younger). This issue was previously communicated in June 2008, August 2009, and April 2011. The FDA is requiring the manufacturers of TNF blockers to perform enhanced safety surveillance for these products. The manufacturers will also provide FDA with annual summaries and assessments of malignancies and TNF blocker utilization data. Healthcare professionals should remain vigilant for cases of malignancy in patients treated with TNF blockers.¹⁰

BACKGROUND

Infliximab is a genetically engineered chimeric human/mouse monoclonal antibody (cA2) against tumor necrosis factor alpha (TNF-α), a key mediator of mucosal inflammation. Increased levels of TNF-α are found in the intestinal mucosa and stool of patients with active Crohn's disease and in the joints of rheumatoid arthritis patients. Elevated TNF-α concentrations are also involved in ulcerative colitis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis. TNF-α activity is neutralized by cA2 antibody binding to the soluble and transmembrane forms which blocks the binding of TNF-α with its receptors. Activities inhibited by anti-TNF-α antibodies include induction of interleukins, enhancement of leukocyte migration, and expression of adhesion molecules. In vitro studies have demonstrated that cells expressing transmembrane TNF-α bound by infliximab are lysed by complement or effector cells. In animal models, antibodies to TNF-α were shown to prevent or reduce inflammation.¹

APPLICABLE CODES

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies may apply.

Coding Clarification: HCPCS code Q5109 is provided for informational purposes only. Ixifi™ (infliximab-qbtX) is currently unavailable in the USA.

HCPCS Code	Description
J1745	Injection, infliximab, excludes biosimilar, 10 mg
Q5103	Injection, infliximab-dyyb, biosimilar, (Inflectra), 10 mg
Q5104	Injection, infliximab-abda, biosimilar, (Renflexis), 10 mg
Q5109	Injection, infliximab-qbtX, biosimilar, (Ixifi), 10 mg

ICD-10 Diagnosis Codes



ICD-10 Diagnosis Codes

Proven/Medically Necessary***Sarcoidosis***

The use of infliximab in patients with chronic pulmonary sarcoidosis was assessed in a multicenter, randomized, double-blind, placebo-controlled study.⁵² Patients must have been treated with at least 10 mg/d of prednisone or equivalent or one or more immunosuppressants for > 3 mo before screening. They received infliximab 3 mg/kg (n=46), 5 mg/kg (n=47), or placebo (n=45) at weeks 0, 2, 6, 12, 18, and 24. They were followed through 52 weeks. The primary endpoint was the change at week 24 from baseline in percent of predicted forced vital capacity (FVC). Patients receiving infliximab 3 or 5 mg/kg had a mean increase of 2.5% compared with no change for those receiving placebo (p=0.038).

Infliximab has also been studied for use in sarcoidosis in small clinical trials. There are additional small published studies and reports that also conclude that clinical evidence supports the use of infliximab for treatment-resistant sarcoidosis.^{6,25,39, 40, 46}

Noninfectious Uveitis

Long-term safety and efficacy of treatment with infliximab in uveitis for more than 1 year in patients (n=164) with Behçet's disease (BD) was evaluated via questionnaire in a retrospective multicenter study.¹² Primary outcome measures assessed were best-corrected VA (BCVA) determined by the Landolt ring, proportion of subjects without relapse of uveitis, frequency of ocular inflammatory attacks per year, and adverse effects of the therapy. The mean age at initiation of infliximab treatment was 42.6±11.7 years, and the mean treatment duration was 32.9±14.4 months. Data before and at the last visit during infliximab treatment were analyzed in 4 groups divided by duration of treatment: group A (n=43, 12-<24 months), group B (n=62, 24-<36 months), group C (n=42, 36-<48 months), and group D (n=17, ≥48 months). The frequency of ocular attacks decreased in all groups (from 5.3±3.0 to 1.0±0.3 in group A, 4.8±4.6 to 1.4±0.3 in group B, 4.1±2.9 to 0.9±0.3 in group C, and 9.5±5.8 to 1.6±0.5 in group D; all P < 0.05). The BCVA was improved in approximately 55% of the eyes after treatment. Mean BCVA was improved after treatment with infliximab in groups A to C (from 0.79±1.04 to 0.59±0.94 in group A, 0.59±1.07 to 0.41±1.04 in group B, and 1.15±1.77 to 0.92±1.73 in group C; all P < 0.05) but not in group D. Uveitis relapsed in 59.1% of all patients after infliximab treatment, and no difference in duration until relapse was observed between individual groups. Approximately 80% of relapses occurred within 1 year after the initiation of infliximab treatment in all groups, 90% of which were controlled by increasing doses of topical corticosteroids and shortening the interval of infliximab infusion. Adverse effects were observed in 65 cases or 35% of all subjects. Infliximab treatment was continued in 85% of the patients, but 15% of the patients discontinued infliximab treatment because of adverse effects or insufficient efficacy. Researchers concluded that this study demonstrated that infliximab reduced the frequency of ocular attacks and improved VA in patients with BD-related uveitis refractory to conventional therapies and was generally well tolerated, with few serious adverse events.

Kruh et al conducted a retrospective, interventional, noncomparative cohort study which evaluated the safety and efficacy of infliximab for the treatment of refractory noninfectious uveitis. Patients (n=88) with chronic, recalcitrant uveitis treated with infliximab were identified through an electronic medical record database.¹³ All charts were reviewed for sex, diagnosis, location of inflammation, presence of vasculitis, prior immunomodulatory treatments, duration of infliximab treatment, dose received, secondary side effects, and other medications continued while receiving treatment with infliximab. The primary outcome measures assessed were the rate of remission, time to remission, relapse rate, failure rate, and patient tolerance. Additional analysis was aimed to identify risk factors that would predict a higher success rate of infliximab to treat various types of noninfectious uveitis. Of the 72 patients (81.8%) who achieved clinical remission while being treated with infliximab, 42 (58.3%) required additional immunomodulatory medications. At 7, 18.1, and 44.7 weeks, 25%, 50%, and 75% of patients, respectively, achieved clinical remission off all corticosteroids. Thirty-two patients (36.4%) experienced at least 1 side effect while on infliximab therapy, and 17 patients (19.3%) discontinued treatment secondary to 1 or more intolerable side effects. The most common adverse effects were skin rash (9.1%) and fatigue (8%). Factors associated with a higher chance to achieve clinical remission were nonidiopathic uveitis (P<0.001), intermediate or panuveitis (P<0.001), absence of vasculitis (P<0.001), and a starting dose ≥5 mg/kg (P<0.011). Researchers concluded that infliximab treatment induced a high rate of complete clinical remission in recalcitrant uveitis and is well tolerated by most patients.

Unproven/Not Medically Necessary***Juvenile Idiopathic Arthritis (Juvenile Rheumatoid Arthritis)***

In an international, multicenter, randomized, placebo-controlled, double-blind study, 122 children with polyarticular juvenile rheumatoid arthritis (JRA) and persistent symptoms despite at least 3 months prior MTX were randomized to receive infliximab 3 mg/kg + MTX or placebo + MTX at weeks 0, 2, and 6.²⁴ At week 14, the placebo group was switched to infliximab 6 mg/kg + placebo. Responses were measured according to American College of Rheumatology Pediatric 30 (Pedi 30) criteria. Although a higher percentage of patients in the 3 mg/kg group achieved responses at

week 14 (63.8% vs. 49.2% in placebo group), the study failed to show the efficacy of infliximab for JRA as the difference was not statistically significant. By week 16, similar percentage response was achieved in both groups. At week 52, the percentages reaching ACR Pedi 50 and ACR Pedi 70 were 69.6% and 51.8%, respectively. The safety profile of infliximab 3 mg/kg was generally less favorable than that of infliximab 6 mg/kg, with more serious adverse events, infusion reactions, antibodies to infliximab, and newly induced antinuclear antibodies and antibodies to double-stranded DNA. Patients who completed the study also continued to receive open-label treatment for up to 2 years.

Infliximab has also been studied for use in JIA in smaller, open-label trials.^{24, 31-34, 36, 43-45} Further large scale studies are required to characterize the efficacy and safety of infliximab in JIA.

Miscellaneous

The medical literature contains a number of small open-label studies and case reports of infliximab therapy for the treatment of adult-onset Still's disease^{26, 27}, Sjogren's syndrome^{22, 28}, graft-vs-host disease²⁹⁻³⁰, myelodysplastic syndromes³⁷, undifferentiated spondyloarthropathy³⁵, Reiter's syndrome¹⁹, hidradenitis suppurativa^{21,49-51}, and Wegener's granulomatosis^{38,47-48}. While these studies and reports showed infliximab to have a positive effect on the manifestations of these diseases, the use of infliximab for these conditions has not been evaluated in large, controlled trials.

Professional Societies

Crohn's Disease

According to the American College of Gastroenterology Practice Guidelines for the Management of Crohn's Disease in Adults (ACG Practice Guidelines) published in February 2009, patients with moderate-severe disease usually have a Crohn's Disease Activity Index (CDAI) of 220-450. They have failed to respond to treatment for mild-moderate disease, or have more prominent symptoms of fever, significant weight loss, abdominal pain or tenderness, intermittent nausea or vomiting (without obstructive findings), or significant anemia.³

The CDAI⁵² is the sum of the following clinical or laboratory variables after multiplying by their weighting factor given in parentheses:

- Number of liquid or soft stools each day for seven days (2);
- Abdominal pain graded from 0-3 in severity each day for seven days (5);
- General well-being, subjectively assessed from 0 = well to 4 = terrible each day for seven days (7);
- Presence of complications, where 1 point is added for each complication (20). Complications include:
 - The presence of joint pains (arthralgia) or frank arthritis
 - Inflammation of the iris or uveitis
 - Presence of erythema nodosum, pyoderma gangrenosum, or aphthous ulcers
 - Anal fissures, fistulae or abscesses
 - Other fistulae (e.g., Enterocutaneous, vesicle, vaginal)
 - Fever (>37.8°C) during the previous week
- Taking diphenoxylate/atropine [Lomotil[®]] or opiates for diarrhea (30);
- Presence of an abdominal mass where 0 = none, 2 = questionable, 5 = definite (10);
- Absolute deviation of hematocrit from 47% in men and 42% in women (6);
- Percentage deviation from standard weight (1)

The ACG Practice Guideline support the use of infliximab for treatment and maintenance of patients with moderate to severely active Crohn's disease who have failed first-line therapy.³

Ulcerative Colitis

According to the American College of Gastroenterology Adult Ulcerative Colitis Practice Guidelines published in March 2010, moderate ulcerative colitis is characterized by more than four stools daily but with minimal signs of toxicity. The guidelines also describe severe disease as more than six bloody stools daily, along with evidence of toxicity such as fever, tachycardia, anemia, or an elevated erythrocyte sedimentation rate. The guidelines further state that the patient with severe colitis refractory to maximal oral treatment with prednisone, oral aminosalicylate drugs, and topical medications may be treated with infliximab if urgent hospitalization is not necessary. Infliximab may also be effective in avoiding colectomy in patients failing intravenous steroids but its long-term efficacy is unknown in this setting.⁴²

Rheumatoid Arthritis

The 2015 American College of Rheumatology (ACR) RA treatment guideline addresses the use of DMARDs, biologics, tofacitinib, and glucocorticoids in early (<6 months) and established (≥ 6 months) RA and the use of various treatment approaches in frequently encountered clinical scenarios, including treat-to-target, switching between therapies, tapering of therapy, the use of biologics and DMARDs in high-risk RA patients, vaccination in patients with

RA receiving DMARDs or biologics, TB screening with biologics or tofacitinib, and laboratory monitoring with DMARDs.² The guideline recommendations apply to common clinical situations, since the panel considered issues common to most patients, not exceptions. Recommendations are classified as either strong or conditional. A strong recommendation means that the panel was confident that the desirable effects of following the recommendation outweigh the undesirable effects (or vice versa), so the course of action would apply to most patients, and only a small proportion would not want to follow the recommendation. A conditional recommendation means that the desirable effects of following the recommendation probably outweigh the undesirable effects, so the course of action would apply to the majority of patients, but some may not want to follow the recommendation. As a result, conditional recommendations are preference sensitive and warrant a shared decision-making approach.

Supplementary Appendix 5, of the 2015 ACR RA guideline, summarizes recommendations for patients with early RA, established RA, and high-risk comorbidities:²

Recommendations for Early RA Patients

- The panel strongly recommends using a treat-to-target strategy rather than a non-targeted approach, regardless of disease activity level. The ideal target should be low disease activity or remission, as determined by the clinician and the patient. In some cases, another target may be chosen because risk tolerance by patients or comorbidities may mitigate the usual choices.
- For DMARD-naïve patients with early, symptomatic RA, the panel strongly recommends DMARD monotherapy over double or triple DMARD therapy in patients with low disease activity and conditionally recommends DMARD monotherapy over double or triple DMARD therapy in patients with moderate or high disease activity. Methotrexate should be the preferred initial therapy for most patients with early RA with active disease.
- For patients with moderate or high disease activity despite DMARD therapy (with or without glucocorticoids), the panel strongly recommends treatment with a combination of DMARDs or a TNFi or a non-TNF biologic, with or without methotrexate (MTX) in no particular order of preference, rather than continuing DMARD monotherapy alone. Biologic therapy should be used in combination with MTX over biologic monotherapy, when possible, due to superior efficacy.
- For patients with moderate or high disease activity despite any of the above DMARD or biologic therapies, the panel conditionally recommends adding low-dose glucocorticoids (defined as ≤ 10 mg/day of prednisone or equivalent). Low-dose glucocorticoids may also be used in patients who need a bridge until realizing the benefits of DMARD therapy. The risk/benefit ratio of glucocorticoid therapy is favorable as long as the dose is low and the duration of therapy is short.
- For patients experiencing a flare of RA, the panel conditionally recommends adding short-term glucocorticoids (< 3 months of treatment) at the lowest possible dose for the shortest possible duration, to provide a favorable benefit-risk ratio for the patient.

Recommendations for Established RA Patients

- The panel strongly recommends using a treat-to-target strategy rather than a non-targeted approach, regardless of disease activity level. The ideal target should be low disease activity or remission, as determined by the clinician and the patient. In some cases, however, another target may be chosen because tolerance by patients or comorbidities may mitigate the usual choices.
- For DMARD-naïve patients with low disease activity, the panel strongly recommends using DMARD monotherapy over a TNFi. For DMARD-naïve patients with moderate or high disease activity, the panel conditionally recommends DMARD monotherapy over double or triple DMARD therapy and DMARD monotherapy over tofacitinib. In general, MTX should be the preferred initial therapy for most patients with established RA with active disease.
- For patients with moderate or high disease activity despite DMARD monotherapy including methotrexate, the panel strongly recommends using combination DMARDs or adding a TNFi or a non-TNF biologic or tofacitinib (all choices with or without methotrexate) in no particular order of preference, rather than continuing DMARD monotherapy alone. Biologic therapy should be used in combination with MTX over biologic monotherapy, when possible, due to its superior efficacy.

For all scenarios for established RA below, treatment may be with or without MTX:

- For moderate or high disease activity despite TNFi therapy in patients currently not on a DMARD, the panel strongly recommends that one or two DMARDs be added to TNFi therapy rather than continuing TNFi therapy alone.
- If disease activity is moderate or high despite single TNFi biologic therapy, the panel conditionally recommends using a non-TNF biologic.
- If disease activity is moderate or high despite non-TNF biologic therapy, the panel conditionally recommends using another non-TNF biologic. However, if a patient has failed multiple non-TNF biologics and they are TNFi-naïve with moderate or high disease activity, the panel conditionally recommends treatment with a TNFi.
- For patients with moderate or high disease activity despite prior treatment with at least one TNFi and at least one non-TNF-biologic (sequentially, not combined), the panel conditionally recommends first treating with another

non-TNF biologic. However, when a non-TNF biologic is not an option (e.g., patient declines non-TNF biologic therapy due to inefficacy or side effects), the panel conditionally recommends treatment with tofacitinib.

- If disease activity is moderate or high despite the use of multiple (2+) TNFi therapies (in sequence, not concurrently), the panel conditionally recommends non-TNF biologic therapy and then conditionally treating with tofacitinib when a non-TNF biologic is not an option.
- If disease activity is moderate or high despite any of the above DMARD or biologic therapies, the panel conditionally recommends adding low-dose glucocorticoids.
- If patients with established RA experience an RA flare while on DMARD, TNFi, or non-TNF biologic therapy, the panel conditionally recommends adding short-term glucocorticoids (< 3 months of treatment) at the lowest possible dose and for shortest possible duration to provide the best benefit-risk ratio for the patient.
- In patients with established RA and low disease activity but not remission, the panel strongly recommends continuing DMARD therapy, TNFi, non-TNF biologic or tofacitinib rather than discontinuing respective medication.
- In patients with established RA currently in remission, the panel conditionally recommends tapering DMARD therapy, TNFi, non-TNF biologic, or tofacitinib.
- The panel strongly recommends not discontinuing all therapies in patients with established RA in disease remission.

Recommendations for RA Patients with High-Risk Comorbidities

Congestive Heart Failure

- In patients with established RA with moderate or high disease activity and New York Heart Association (NYHA) class III or IV congestive heart failure (CHF), the panel conditionally recommends using combination DMARD therapy, a non-TNF biologic, or tofacitinib rather than a TNFi.
- If patients in this population are treated with a TNFi and their CHF worsens while on the TNFi, the panel conditionally recommends switching to combination DMARD therapy, a non-TNF biologic, or tofacitinib rather than a different TNFi.

Hepatitis B

- In patients with established RA with moderate or high disease activity and evidence of active hepatitis B infection (hepatitis surface antigen positive > 6 months), who are receiving or have received effective antiviral treatment, the panel strongly recommends treating them the same as patients without this condition.
- For a patient with natural immunity from prior exposure to hepatitis B (i.e., HB core antibody and HBS antibody positive and normal liver function tests), the panel recommends the same therapies as those without such findings as long as the patient's viral load is monitored.
- For patients with chronic hepatitis B who are untreated, referral for antiviral therapy is appropriate prior to immunosuppressive therapy.

Hepatitis C

- In patients with established RA with moderate or high disease activity and evidence of chronic hepatitis C virus (HCV) infection, who are receiving or have received effective antiviral treatment, the panel conditionally recommends treating them the same as the patients without this condition.
- The panel recommends that rheumatologists work with gastroenterologists and/or hepatologists who would monitor patients and reassess the appropriateness of antiviral therapy. This is important considering the recent availability of highly effective therapy for HCV, which may lead to a greater number of HCV patients being treated successfully.
- If the same patient is not requiring or receiving antiviral treatment for their hepatitis C, the panel conditionally recommends using DMARD therapy rather than TNFi.

Malignancy

- Previous Melanoma and Non-Melanoma Skin Cancer
 - In patients with established RA and moderate or high disease activity and a history of previously treated or untreated skin cancer (melanoma or non-melanoma), the panel conditionally recommends the use of DMARD therapy over biologics or tofacitinib.
- Previous Lymphoproliferative Disorders
 - In patients with established RA with moderate or high disease activity and a history of a previously treated lymphoproliferative disorder, the panel strongly recommends using rituximab rather than a TNFi and conditionally recommends using combination DMARD therapy, abatacept or tocilizumab rather than TNFi.
- Previous Solid Organ Cancer
 - In patients with established RA with moderate or high disease activity and previously treated solid organ cancer, the panel conditionally recommends that they be treated for RA just as one would treat an RA patient without a history of solid organ cancer.

Serious Infections

- In patients with established RA with moderate or high disease activity and previous serious infection(s), the panel conditionally recommends using combination DMARD therapy or abatacept rather than TNFi.

Plaque Psoriasis

The American Academy of Dermatology (AAD) defines moderate to severe psoriasis as affecting more than 5% of the body surface area (BSA) or affecting crucial body areas such as the hands, feet, face, or genitals. According to the AAD Practice Guidelines for the management of psoriasis, the potential importance of TNF- α in the pathophysiology of psoriasis is underscored by the observation that there are elevated levels of TNF- α in both the affected skin and serum of patients with psoriasis. These elevated levels have a significant correlation with psoriasis severity as measured by the PASI score. Furthermore, after successful treatment of psoriasis, TNF- α levels are reduced to normal levels. The guidelines support the use of infliximab for psoriasis based on evidence ranked as consistent, good quality, and patient-oriented (Strength of Recommendation: A).¹⁸

Psoriatic Arthritis

The American Academy of Dermatology (AAD) defines psoriatic arthritis (PsA) as mild, moderate, or severe. Where mild disease responds to NSAIDs, moderate disease requires DMARDs or TNF blockers. Appropriate treatment of severe PsA requires DMARDs plus TNF blockers or other biologic therapies. If PsA is diagnosed, treatment should be initiated to alleviate signs and symptoms of PsA, inhibit structural damage, and maximize quality of life (QOL). According to the AAD Practice Guidelines for the management of psoriatic arthritis, the potential importance of TNF- α in the pathophysiology of PsA is underscored by the observation that there are elevated levels of TNF- α in the synovium, joint fluid, and skin of patients with PsA. The guidelines support the use of infliximab for PsA based on evidence ranked as consistent, good quality, and patient-oriented. (Strength of Recommendation: A).¹⁶

Ankylosing Spondylitis

Evidence based recommendations for the management of ankylosing spondylitis (AS) were created as a combined effort of the 'Assessment in AS' international working group and the European League Against Rheumatism (EULAR). According to these comprehensive guidelines, anti-TNF treatment (infliximab, etanercept, adalimumab, and golimumab) should be given to patients with persistently high disease activity despite conventional treatments. There is no evidence to support the obligatory use of DMARDs before, or concomitant with, anti-TNF treatment in patients with axial disease. There is no evidence to support a difference in efficacy of the various TNF inhibitors on the axial and articular/enthesal disease manifestations; but in the presence of IBD a difference in gastrointestinal efficacy needs to be taken into account. Switching to a second TNF blocker might be beneficial especially in patients with loss of response.⁸

Juvenile Idiopathic Arthritis

The 2011 American College of Rheumatology (ACR) Recommendations for the Treatment of Juvenile Idiopathic Arthritis include the tumor necrosis factor (TNF) inhibitors adalimumab, etanercept, infliximab and do not differentiate between the agents.³⁴

For JIA patients with history of arthritis of 4 or fewer joints:

- Initiation of a TNF inhibitor was recommended for patients who have received glucocorticoids joint injections and 3 months of methotrexate at the maximum tolerated typical dose and have moderate or high disease activity and features of poor prognosis (level C).
- Initiation of a TNF inhibitor was also recommended for patients who have received glucocorticoids joint injections and 6 months of methotrexate and have high disease activity without features of poor prognosis (level C).
- Initiation of a TNF inhibitor was recommended for patients specifically with the enthesitis-related arthritis category of JIA who have received glucocorticoids joint injections and an adequate trial of sulfasalazine (without prior methotrexate) and have moderate or high disease activity, irrespective of prognostic features (level C).

For JIA patients with history of arthritis of 5 or more joints:

- Initiation of a TNF inhibitor was recommended for patients who have received methotrexate or leflunomide for 3 months at the maximum tolerated typical dose and have moderate or high disease activity, irrespective of poor prognostic features (level B).
- Initiation of a TNF inhibitor was also recommended for patients who have received methotrexate or leflunomide for 6 months and have low disease activity, irrespective of poor prognostic features (level B).
- Switching from one TNF inhibitor to another was recommended as one treatment approach for patients who have received the current TNF inhibitor for 4 months and have moderate or high disease activity, irrespective of poor prognostic features (level C).
- Switching to a TNF inhibitor was recommended as one treatment approach for patients who have received abatacept for 3 months and have high disease activity and features of poor prognosis and for patients who have

received abatacept for 6 months and have moderate or high disease activity, irrespective of prognostic features (level D).

Level of evidence "B" was assigned when the recommendation was supported by nonrandomized controlled studies (e.g., cohort and case-control studies) or extrapolations from randomized clinical trials.

Level of evidence "C" was assigned when the recommendation was supported by uncontrolled studies (case series), extrapolations from nonrandomized controlled studies, or marked extrapolations from randomized clinical trials (e.g., studies of adult arthritis patients applied to juvenile arthritis or studies of polyarthritis phenotype applied to oligoarthritis).

Noninfectious Uveitis

In 2014, a subcommittee of the Executive Committee of the American Uveitis Society conducted a systematic review of published literature and developed a guideline for the use of anti-tumor necrosis factor α (TNF- α) biologic agents in patients with ocular inflammatory disorders. These recommendations are as follows:

- Strong recommendation. Anti-TNF therapy with infliximab (good-quality evidence) or adalimumab (moderate-quality evidence) should be considered early in management of patients with vision threatening ocular manifestations of Behçet's disease.
- Strong recommendation. Anti-TNF therapy with infliximab (good-quality evidence) or adalimumab (good-quality evidence) should be considered as second-line immunomodulatory therapy for children with vision-threatening uveitis secondary to JIA in whom methotrexate therapy is insufficiently effective or not tolerated. Methotrexate therapy, if tolerated, may be combined with infliximab therapy.
- Strong recommendation. Anti-TNF therapy with infliximab or potentially adalimumab should be considered as second-line immunomodulatory therapy in patients with vision-threatening chronic uveitis from seronegative spondyloarthropathy (good-to moderate-quality evidence).
- Discretionary recommendation. Anti-TNF therapy with infliximab or adalimumab for other forms of ocular inflammation, including sarcoidosis, scleritis, and panuveitis, may be considered in patients with vision-threatening, corticosteroid-dependent disease who have failed first-line immunomodulatory therapies such as antimetabolites or calcineurin inhibitors (moderate-quality evidence). The literature for adalimumab is less developed than for infliximab, but these agents seem to show similar efficacy in most studies. Until more comparative data are available, no recommendation can be made as to preferred agent, although numerous studies have suggested that adalimumab may be effective in patients who have become intolerant to or have developed reduced clinical responsiveness to infliximab.
- Strong recommendation. Use of infliximab or adalimumab should be considered before etanercept therapy for treatment of ocular inflammatory disease. Etanercept may have efficacy for treatment of some forms of ocular inflammatory disease such as mucocutaneous Behçet's disease, but it has been associated with development of uveitis in JIA patients and development of sarcoid-like disease in others. Patients presently taking etanercept for other indications with existing, incompletely controlled uveitis or new ocular inflammatory disease should consider switching to infliximab or adalimumab if possible.

REFERENCES

The foregoing Oxford policy has been adapted from an existing UnitedHealthcare Pharmacy, Clinical Pharmacy Program that was researched, developed and approved by the UnitedHealth Group National Pharmacy & Therapeutics Committee. [2018D0004W]

1. Remicade [prescribing information]. Horsham, PA: Janssen Biotech Inc.; October 2017.
2. Singh JA, Saag KG, Bridges SL, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Care & Research. Arthritis Rheum.* 2016;68(1):1-26.
3. Lichtenstein GR, Hanauer SB, Sandborn WJ, et al. American College of Gastroenterology Practice Guidelines. Management of Crohn's Disease in Adults. *Am J Gastroenterol.* 2009;104(2):465-83.
4. Lichtenstein GR, Abreu MT, Cohen R, Tremaine W. American Gastroenterological Association Institute medical position statement on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease. *Gastroenterology.* 2006;130(3):935-9.
5. MCG™ Care Guidelines, Ambulatory Care, 22nd Edition. Infliximab. Accessed on February 14, 2018.
6. Yee AM, Pochapin MB. Treatment of complicated sarcoidosis with infliximab anti-tumor necrosis factor-alpha therapy. *Ann Intern Med.* 2001;135(1):27-31.
7. Zochling J, van der Heijde D, Burgos-Vargas R, et al. ASAS/EULAR recommendations for the management of Ankylosing Spondylitis. *Ann Rheum Dis.* 2006 65:442-452.

8. Braun J, van den Berg R, Baraliakos X, et al. 2010 Update of the ASAS/EULAR Recommendations for the Management of Ankylosing Spondylitis. *Ann Rheum Dis*. 2011;70(6):896-904.
9. U.S. Food and Drug Administration Information for Healthcare Professionals: Tumor Necrosis Factor (TNF) Blockers (marketed as Remicade, Enbrel, Humira, Cimzia, and Simponi). <https://www.fda.gov/Drugs/DrugSafety/ucm109340.htm>. Accessed July 1, 2013.
10. U.S. Food and Drug Administration Drug Safety Communication: UPDATE on Tumor Necrosis Factor (TNF) blockers and risk for pediatric malignancy. <http://www.fda.gov/Drugs/DrugSafety/ucm278267.htm>. Accessed July 1, 2013.
11. U.S. Food and Drug Administration Drug Safety Communication: Drug labels for the Tumor Necrosis Factor-alpha (TNF α) blockers now include warnings about infection with Legionella and Listeria bacteria. <http://www.fda.gov/Drugs/DrugSafety/ucm270849.htm>. Accessed July 1, 2013.
12. Takeuchi M, Kezuka T, Sugita S, et al. Evaluation of the long-term efficacy and safety of infliximab treatment for uveitis in Behçet's disease: a multicenter study. *Ophthalmology*. 2014 Oct;121(10):1877-84.
13. Kruh JN, Yang P, Suelves AM, et al. Infliximab for the treatment of refractory noninfectious Uveitis: a study of 88 patients with long-term follow-up. *Ophthalmology*. 2014 Jan;121(1):358-64.
14. Levy-Clark G, Jabs DA, Read RW, et al. Expert panel recommendations for the use of anti-tumor necrosis factor biologic agents in patients with ocular inflammatory disorders. *Ophthalmology*. 2014 Mar;121(3):785-96.
15. Lee FF, Foster CS. Pharmacology of uveitis. *Expert Opin Pharmacother*. 2010;11(7):1135-1146.
16. Gottlieb A, Korman NJ, Gordon KB, et al. American Academy of Dermatology Guidelines for the Care and Management of Psoriasis and Psoriatic Arthritis. Section 2: Psoriatic arthritis: Overview and guidelines of care for treatment with an emphasis on the biologics. *J Am Acad Dermatol*. 2008;58(5):851-64.
17. Hatemi G, et al. EULAR recommendations for the management of Behçet disease. *Annals of the Rheumatic Diseases* 2008;67(12):1656-62.
18. Menter A, Gottlieb A, Feldman SR, et al. American Academy of Dermatology Guidelines for the Care and Management of Psoriasis and Psoriatic Arthritis. Section 1: Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. *J Am Acad Dermatol*. 2008;58(5):826-50.
19. Gaylis N. Infliximab in the treatment of an HIV positive patient with Reiter's syndrome. *J Rheumatol*. 2003;30(2):407-411.
20. Murphy CC, Ayliffe WH, Booth A, et al. Tumor necrosis factor alpha blockade with infliximab for refractory uveitis and scleritis. *Ophthalmology*. 2004;111(2):352-356.
21. Sullivan TP, Welsh E, Kerdel FA, et al. Infliximab for hidradenitis suppurativa. *Br J Dermatol*. 2003;149(5):1046-1049.
22. Mariette X, Ravaud P, Steinfeld S, et al. Inefficacy of infliximab in primary Sjogren's syndrome: results of the randomized, controlled Trial of Remicade in Primary Sjogren's Syndrome (TRIPSS). *Arthritis Rheum*. 2004;50(4):1270-1276.
23. Ruperto N, Lovell DJ, Cuttica R, et al. A randomized, placebo-controlled trial of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis. *Arthritis Rheum*. 2007;56(9):3096-106.
24. Russo RA, Katsicas MM. Clinical remission in patients with systemic juvenile idiopathic arthritis treated with anti-tumor necrosis factor agents. *J Rheumatol*. 2009;36(5):1078-82.
25. Baughman RP, Lower EE. Infliximab for refractory sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis*. 2001;18(1):70-74.
26. Kraetsch HG, Antoni C, Kalden JR, Manger B. Successful treatment of a small cohort of patients with adult onset Still's Disease with infliximab: first experiences. *Ann Rheum Dis*. 2001;60(suppl 3):iii55-57.
27. Cavagna L, Caporali R, Epis O, et al. Infliximab in the treatment of adult Still's Disease refractory to conventional therapy. *Clin Exp Rheumatol*. 2001;19(3):329-332.
28. Steinfeld SD, Demols P, Salmon I, et al. Infliximab in patients with primary Sjogren's Syndrome: a pilot study. *Arthritis Rheum*. 2001;44(10):2371-2375.
29. Kobbe G, Schneider P, Rohr U, et al. Treatment of severe steroid refractory acute graft-vs-host disease with infliximab, a chimeric human/mouse antiTNF α antibody. *Bone Marrow Transplant*. 2001;28(1):47-49.
30. Rivkina AM, Stump LS. Infliximab in graft-versus-host disease. *Am J Health-Syst Pharm*. 2002;59(13):1271-1275.
31. Tynjälä P, Vähäsalo P, Tarkiainen M, et al. Aggressive Combination Drug Therapy in Very Early Polyarticular Juvenile Idiopathic Arthritis (ACUTE-JIA): a multicentre randomized open-label clinical trial. *Ann Rheum Dis*. 2011 Sep;70(9):1605-12. Epub 2011 May 28.

32. Lamot L, Bukovac LT, Vidovic M, et al. The 'head-to-head' comparison of etanercept and infliximab in treating children with juvenile idiopathic arthritis. *Clin Exp Rheumatol*. 2011 Jan-Feb;29(1):131-9. Epub 2011 Feb 23.
33. Ruperto N, Lovell DJ, Cuttica R, et al. Long-term efficacy and safety of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis: findings from an open-label treatment extension. *Ann Rheum Dis*. 2010 Apr;69(4):718-22.
34. Beukelman T, Patkar NM, Saag KG, et al. 2011 American College of Rheumatology Recommendations for the Treatment of Juvenile Idiopathic Arthritis: Initiation and Safety Monitoring of Therapeutic Agents for the Treatment of Arthritis and Systemic Features. *Arthritis Care & Research*. 2011 April;63(4):465-82.
35. Brandt J, Haibel H, Reddig J, et al. Successful short term treatment of severe undifferentiated spondyloarthritis with anti-tumor necrosis factor-monoclonal antibody infliximab. *J Rheumatol*. 2002;29(1):118-122.
36. De Marco G, Gerloni V, Pontikaki I, et al. Long-term evaluation of infliximab in the treatment of persistently active juvenile idiopathic arthritis refractory to conventional therapy. *Reumatismo*. 2007;59(1):50-6.
37. Stasi R, Amadori S. Infliximab chimaeric anti-tumour necrosis factor alpha monoclonal antibody treatment for patients with myelodysplastic syndromes. *Br J Haematol*. 2002;116(2):334-337.
38. Lamprecht P, Voswinkel J, Lienthal T, et al. Effectiveness of TNF-alpha blockade with infliximab in refractory Wegener's granulomatosis. *Rheumatology*. 2002;41(11):1303-1307.
39. Doty JD, Mazur JE, Judson MA. Treatment of sarcoidosis with infliximab. *Chest*. 2005;127(3):1064-71.
40. Ulbricht KU, Stoll M, Bierwirth J, et al. Successful tumor necrosis factor alpha blockade treatment in therapy-resistant sarcoidosis. *Arthritis Rheum*. 2003; 48(12):3542-3.
41. Yoshida EM. The Crohn's Disease Activity Index, its derivatives and the Inflammatory Bowel Disease Questionnaire: A review of instruments to assess Crohn's disease. *Can J Gastroenterol*. 1999;13(1):65-73.
42. Kornbluth A. Ulcerative Colitis Practice Guidelines in Adults: American College of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol*. 2010;105:501-523.
43. Katsicas MM, Russo RA. Use of infliximab in patients with systemic juvenile idiopathic arthritis refractory to etanercept. *Clin Exp Rheumatol*. 2005;23(4):545-8.
44. Gerloni V, Pontikaki I, Gattinara M, et al. Efficacy of repeated intravenous infusions of an anti-tumor necrosis factor alpha monoclonal antibody, infliximab, in persistently active, refractory juvenile idiopathic arthritis: results of an open-label prospective study. *Arthritis Rheum*. 2005;52(2):548-53.
45. Lahdenne P, Vahasalo P, Honkanen V. Infliximab or etanercept in the treatment of children with refractory juvenile idiopathic arthritis: an open label study. *Ann Rheum Dis*. 2003;62(3):245-7.
46. Doherty CB, Rosen T. Evidence-based therapy for cutaneous sarcoidosis. *Drugs*. 2008;68(10):1361-83.
47. Bartolucci P, Ramanoelina J, Cohen P, et al. Efficacy of the anti-TNF-alpha antibody infliximab against refractory systemic vasculitides: an open pilot study on 10 patients. *Rheumatology (Oxford)*. 2002;41(10):1126-32.
48. Kleinert J, Lorenz M, Kostler W, et al. Refractory Wegener's granulomatosis responds to tumor necrosis factor blockade. *Win Klin Wochenschr*. 2004;116(9-10):334-8.
49. Roussomoustakaki M, Dimoulios P, Chatzicostas C, et al. Hidradentis suppurativa associated with Crohn's disease and spondyloarthritis: response to anti-TNF therapy. *J Gastroenterol*. 2003;38(10):1000-4.
50. Rosi YL, Lowe L, Kang S. Treatment of hidradentis suppurativa with infliximab in a patient with Crohn's disease. *J Dermatolog Treat*. 2005;16(1):58-61.
51. Fardet L, Dupuy A, Kerob D, et al. Infliximab for severe hidradentis suppurativa: transient clinical efficacy in 7 consecutive patients. *J Am Acad Dermatol*. 2007;56(4):624-8.
52. Baughman RP, Drent M, Kavuru M, et al. Infliximab therapy in patients with chronic sarcoidosis and pulmonary involvement. *Am J Respir Crit Care Med*. 2006;174(7):795-802.
53. Menter A, Korman NJ, Elmets CA, et al. American Academy of Dermatology Guidelines for the Care and Management of Psoriasis and Psoriatic Arthritis. Section 5: Guidelines of care for the treatment of psoriasis with phototherapy and photochemotherapy. *J Am Acad Dermatol*. 2010;62:114-35.
54. Menter A, Korman NJ, Elmets CA, et al. American Academy of Dermatology Guidelines for the Care and Management of Psoriasis and Psoriatic Arthritis. Section 3: Overview of psoriasis and guidelines of care for the treatment of psoriasis with topical therapies. *J Am Acad Dermatol*. 2009;60:643-59.
55. Menter A, Korman NJ, Elmets CA, et al. American Academy of Dermatology Guidelines for the Care and Management of Psoriasis and Psoriatic Arthritis. Section 4: Overview of psoriasis and guidelines of care for the treatment of psoriasis with traditional systemic agents. *J Am Acad Dermatol*. 2009;61:451-85.

56. Xeljanz [package insert]. New York, NY: Pfizer Labs; December 2017.
57. Inflectra [prescribing information]. New York, NY: Pfizer; August 2016.
58. Yoo DH, Hrycaj P, Miranda P, et al. A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study. *Ann Rheum Dis*. 2013 Oct;72(10):1613-20.
59. Park W, Hrycaj P, Jeka S, et al. A randomised, double-blind, multicentre, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study. *Ann Rheum Dis*. 2013 Oct;72(10):1605-12.
60. Gecse KB, Lovász BD, Farkas K et al. Efficacy and Safety of the Biosimilar Infliximab CT-P13 Treatment in Inflammatory Bowel Diseases: A Prospective, Multicentre, Nationwide Cohort. *J Crohns Colitis*. 2016 Feb;10(2):133-40.
61. Ruiz-Argüello MB, Maguregui A, Ruiz Del Agua A, et al. Antibodies to infliximab in Remicade-treated rheumatic patients show identical reactivity towards biosimilars. *Ann Rheum Dis*. 2016 Sep;75(9):1693-6.
62. Renflexis [prescribing information]. Kenilworth, NJ: Merck Sharp & Dohme Corp; April 2017.
63. Choe JY, Prodanovic N, Niebrzydowski J, et al. A randomised, double-blind, phase III study comparing SB2, an infliximab biosimilar, to the infliximab reference product Remicade in patients with moderate to severe rheumatoid arthritis despite methotrexate therapy. *Ann Rheum Dis*. 2017 Jan;76(1):58-64.

POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
01/01/2019	<ul style="list-style-type: none"> • Updated list of applicable HCPCS codes to reflect annual code edits: <ul style="list-style-type: none"> ○ Added Q5109 with corresponding notation to indicate code is provided for informational purposes only; Ixifi™ (infliximab-qbtx) is currently unavailable in the USA • Archived previous policy version PHARMACY 067.34 T2