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

<table>
<thead>
<tr>
<th>Applicable Lines of Business/Products</th>
<th>This policy applies to Oxford Commercial plan membership.</th>
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<tr>
<td>Benefit Type</td>
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<tr>
<td>Referral Required</td>
<td>Yes - Office</td>
</tr>
<tr>
<td>(Does not apply to non-gatekeeper products)</td>
<td>No - Outpatient, Home</td>
</tr>
<tr>
<td>Authorization Required</td>
<td>Yes - Outpatient, Home¹ ² Yes – Office¹ ²</td>
</tr>
<tr>
<td>(Precertification always required for inpatient admission)</td>
<td>Yes¹ ²</td>
</tr>
<tr>
<td>Pre-certification with Medical Director Review Required</td>
<td>Office, Outpatient, Home</td>
</tr>
</tbody>
</table>

¹Precertification 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.
²Precertification with review by a Medical Director or their designee is required for Inflectra and Renflexis in all settings/sites of service.
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)

A. Preferred Product

Remicade® (infliximab) is the preferred infliximab product. Coverage will be provided for Remicade® contingent on the coverage criteria in section B.

Coverage for Inflectra™ (infliximab-dyyb) or Renflexis™ (infliximab-abda) will be provided contingent on the criteria in this section and the coverage criteria in section B. 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.
    - 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.
  - 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.
- 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
B. **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, aminosalicylate, 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.

2. **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.

3. **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.

4. **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.

5. **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.

6. **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.

7. **Psoriatic arthritis:**
   - Reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in patients with psoriatic arthritis.

8. **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:

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.

2. **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.

3. **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.

4. **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.

5. **Ankylosing spondylitis:**
   - Reducing signs and symptoms in patients with active disease.

6. **Psoriatic arthritis:**
   - Reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in patients with psoriatic arthritis.

7. **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.

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<th>HCPCS Code</th>
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</tr>
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**ICD-10 Diagnosis Codes**

| ICD_10 Diagnosis Code table.xls |

**CLINICAL EVIDENCE**

**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

Noninfective 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 inpatients 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 of 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\(^{26,27}\), Sjögren's syndrome\(^{22,28}\), graft-vs-host disease\(^{29-30}\), myelodysplastic syndromes\(^{37}\), undifferentiated spondyloarthropathy\(^{35}\), Reiter's syndrome\(^{19}\), hidradenitis suppurativa\(^{21,49-51}\), and Wegener's granulomatosis\(^{38,67-48}\). 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 CDAI\(^{52}\) 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\(^{[9]}\)] 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**

An American College of Rheumatology (ACR) working group has reported 2012 updates to their 2008 recommendations on the use of DMARDs and biologic agents in patients with RA\(^4\). Highlights of the updated ACR recommendations are as follows:

For Early RA (disease duration < 6 months):
- In patients with early RA, the Task Force Panel (TFP) recommends the use of an anti-TNF biologic with or without methotrexate in patients who have high disease activity with poor prognostic features. Infliximab is the only exception and the recommendation is to use it in combination with methotrexate, but not as monotherapy.

For Established RA (disease duration ≥ 6 months or meeting the 1987 ACR classification criteria):
- If a patient has moderate or high disease activity after 3 months of methotrexate monotherapy or DMARD combination therapy, as an alternative to the DMARD recommendation just noted above, the panel recommends adding or switching to an anti-TNF biologic, abatacept, or rituximab.
- If after 3 months of intensified DMARD combination therapy or after a second DMARD, a patient still has moderate or high disease activity, add or switch to an anti-TNF biologic.
• If a patient still has moderate or high disease activity after 3 months of anti-TNF biologic therapy and this is due to a lack or loss of benefit, switching to another anti-TNF biologic or a non-TNF biologic is recommended.
• If a patient still has moderate or high disease activity after 6 months of a non-TNF biologic and the failure is due to a lack or loss of benefit, switch to another non-TNF biologic or an anti-TNF biologic.
• If a patient has high disease activity after failing an anti-TNF biologic because of a serious adverse event, switch to a non-TNF biologic.
• If a patient has moderate or high disease activity after failing an anti-TNF biologic because of a nonserious adverse event, switch to another anti-TNF biologic or a non-TNF biologic. If a patient has moderate or high disease activity after failing a non-TNF biologic because of an adverse event (serious or nonserious), switch to another non-TNF biologic or an anti-TNF biologic.
• Indications for starting or resuming DMARDs or biologic agents included the goal of targeting low disease activity and achieving remission in all patients with new RA.

**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/entheseal 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. There 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 (moderate-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. [2017D0004U]


POLICY HISTORY/REVISION INFORMATION

<table>
<thead>
<tr>
<th>Date</th>
<th>Action/Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>08/01/2017</td>
<td>Changed policy title; previously titled Infliximab (Remicade® and Inflectra™)</td>
</tr>
<tr>
<td></td>
<td>Revised conditions of coverage/authorization requirements; added language to</td>
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<td></td>
<td>indicate precertification with review by a Medical Director or their designee is</td>
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<tr>
<td></td>
<td>required in all settings/sites of service for Renflexis</td>
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<tr>
<td></td>
<td>Revised coverage rationale:</td>
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<tr>
<td></td>
<td>- Updated list of infliximab products addressed in this policy; added Renflexis™</td>
</tr>
<tr>
<td></td>
<td>(infliximab-abda)</td>
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<tr>
<td></td>
<td>- Updated language pertaining to preferred products:</td>
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<td></td>
<td>- Removed language indicating:</td>
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<tr>
<td></td>
<td>- Members must use Remicade® unless the criteria listed in the</td>
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<tr>
<td></td>
<td>Preferred Product Criteria section of the policy are met, prior to being</td>
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<tr>
<td></td>
<td>approved to use Inflectra™ (infliximab-dyyb) or any other infliximab</td>
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<td></td>
<td>biosimilar product</td>
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<td></td>
<td>- Members already on Inflectra™ (infliximab-dyyb) will be required to</td>
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<td>change therapy to Remicade® (infliximab) unless they meet the</td>
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<tr>
<td></td>
<td>criteria listed in the Preferred Product Criteria section of the policy</td>
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<td></td>
<td>- Added language to indicate:</td>
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<td>- Coverage will be provided for Remicade® contingent on the coverage</td>
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<td></td>
<td>criteria listed in the Diagnosis-Specific Criteria section of the policy</td>
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<td>- Coverage for Inflectra™ (infliximab-dyyb) or Renflexis™ (infliximab-</td>
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<td>abda) will be provided contingent on the criteria listed in the</td>
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<td></td>
<td>Preferred Product Criteria and Diagnosis-Specific Criteria sections of the</td>
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<td>policy</td>
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<tr>
<td></td>
<td>- In order to continue coverage, members already on Inflectra™ or Renflexis™</td>
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<td></td>
<td>will be required to change therapy to Remicade® unless they meet the</td>
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<td></td>
<td>criteria listed in the Preferred Product Criteria section of the policy</td>
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<tr>
<td></td>
<td>- Renflexis™ (infliximab-abda) is medically necessary for the</td>
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<td>indications specified in this policy when the listed criteria are met</td>
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<tr>
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</tbody>
</table>
|      | - Updated list of applicable HCPCS codes; revised description for Q5102:  
|      |   o Added modifier ZB to denote drug manufacturer "Pfizer"  
|      |   o Added duplicate code without modifier to denote drug manufacturer "Merck"  
|      | - Updated supporting information to reflect the most current FDA information and references  
|      |   o Replaced reference to "MCG® Ambulatory Care 19th Edition" with "MCG™ Care Guidelines, Ambulatory Care, 21st Edition"  
|      | - Archived previous policy version PHARMACY 067.29 T2 |