INFLIXIMAB (AVSOLA™, INFLECTRA®, REMICADE®, & RENFLEXIS®)

Policy Number: PHARMACY 067.40 T2 **Effective Date**: February 1, 2020

Instructions for Use

Table of Contents **Page**

Related Policies

- Acquired Rare Disease Drug Therapy Exception Process
- Experimental/Investigational Treatment
- Experimental/Investigational Treatment for NJ Plans
- Maximum Dosage
- Provider Administered Drugs – Site of Care
- Review at Launch for New to Market Medications
- Specialty Pharmacy for Certain Specialty Medications Administered in an Outpatient Hospital Setting

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)	No
Authorization Required (Precertification always required for inpatient admission)	Yes[5]
Precertification with Medical Director Review Required	Yes[5]
Applicable Site(s) of Service (If site of service is not listed, Medical Director review is required)	Office[4], Outpatient[1,2], Home[3]
Special Considerations	[1]Additional precertification requirements apply to requests for hospital outpatient facility infusion of Inflectra, Remicade, and Renflexis; refer to the Clinical Policy titled Provider Administered Drugs - Site of Care. [2]Participating 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 Clinical Policy titled Specialty Pharmacy for Certain Specialty Medications Administered in an Outpatient Hospital Setting for additional information. [3]Home infusion of infliximab requires additional precertification for the home care services. [4]**Participating providers in the office setting:** Precertification is required for services performed in the office of a participating provider. **Non-participating/ out-of-network providers in the office setting**: Precertification is not required, but encouraged for out-of-network services performed in the office. If

Special Considerations *(continued)*	precertification is not obtained, Oxford will review for out-of-network benefits and medical necessity after the service is rendered. [5]Precertification is not required, however it is strongly recommended for **Avsola**. While no penalty will be imposed for failure to request a pre-service review, if one is not requested, a medical necessity review will be conducted post-service to determine coverage. It is the referring physician's responsibility to provide medical documentation to demonstrate clinical necessity for the medication. As of **May 1, 2020**, precertification **will** be required. Refer to Clinical Policy titled Review at Launch for New to Market Medications.

COVERAGE RATIONALE

See Benefit Considerations

Avsola (infliximab-axxq) has been added to the Review at Launch program. Some members may not be eligible for coverage of this medication at this time. Reference the Clinical Policy titled Review at Launch for New to Market Medications for additional details.

This policy refers to the following infliximab products:
- Avsola™ (infliximab-axxq)
- Remicade® (infliximab)
- Inflectra® (infliximab-dyyb)
- Renflexis® (infliximab-abda)

Preferred Product

Inflectra® (infliximab-dyyb) and Remicade® (infliximab) are the preferred infliximab products. Coverage will be provided for Inflectra® or Remicade® contingent on the coverage criteria in the *Diagnosis-Specific Criteria* section.

Coverage for Avsola™ (infliximab-axxq) and 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 Avsola™ or Renflexis® will be required to change therapy to Inflectra® or Remicade® unless they meet the criteria in this section.

Preferred Product Criteria

Treatment with Avsola, Renflexis, or other infliximab biosimilar is medically necessary for the indications specified in this policy when BOTH of the following criteria are met:
- **One** of the following:
  - **Both** of the following:
    - History of a trial of at least 14 weeks of **both** Inflectra and 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 Avsola, Renflexis, or other infliximab biosimilar product, than experienced with Inflectra and Remicade

  or
  - **Both** of the following:
    - History of intolerance, contraindication, or adverse event to Inflectra and Remicade
    - Physician attests that in their clinical opinion the same intolerance, contraindication, or adverse event would not be expected to occur with Avsola, Renflexis, 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 Inflectra, Remicade, or other infliximab biosimilar 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; **and**
    - Systemic corticosteroids; **and**
    - 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
- **Immune checkpoint inhibitor-related toxicities when BOTH of the following criteria are met**:[67]
  - Patient has recently received checkpoint inhibitor therapy [e.g., Keytruda (Pembrolizumab), Opdivo (Nivolumab)]; **and**
  - **One** of the following:
    - **Both** of the following:
      - Diagnosis of moderate (G2) or severe (G3-4) immunotherapy-related diarrhea or colitis; **and**
      - History of failure, contraindication, or intolerance to corticosteroids (e.g. methylprednisolone)

      or
    - **Both** of the following:
      - Diagnosis of severe (G3-4) immunotherapy-related pneumonitis; **and**
      - History of failure, contraindication, or intolerance to corticosteroids (e.g. methylprednisolone)

      or
    - **Both** of the following:
      - Diagnosis of severe (G3) or life-threatening (G4) immunotherapy-related acute renal failure/elevated serum creatinine; **and**
      - Toxicity remains >G2 after 1 week of corticosteroids

      or
    - **Both** of the following:
      - Diagnosis of severe (G3-4) immunotherapy-related uveitis; **and**
      - Toxicity remains after 1 week of high dose systemic corticosteroids

      or
    - **Both** of the following:
      - Diagnosis of life threatening (G4) immunotherapy-related myocarditis, pericarditis, arrhythmias, or impaired ventricular function; **and**
      - No improvement of toxicity within 24 hours of starting pulse-dose methylprednisolone

      or

- **Both** of the following:
  - Diagnosis of severe immunotherapy-related inflammatory arthritis; **and**
  - No symptom improvement within 2 weeks of starting high-dose corticosteroids

There may be other conditions that qualify as serious, rare diseases for which the use of infliximab may be appropriate. Refer to the Benefit Considerations section of this policy for additional information.

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

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

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.

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
J3490	Unclassified drugs
J3590	Unclassified biologics
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	Description
D86.0	Sarcoidosis of lung
D86.1	Sarcoidosis of lymph nodes
D86.2	Sarcoidosis of lung with sarcoidosis of lymph nodes
D86.3	Sarcoidosis of skin
D86.81	Sarcoid meningitis
D86.82	Multiple cranial nerve palsies in sarcoidosis
D86.83	Sarcoid iridocyclitis
D86.84	Sarcoid pyelonephritis
D86.85	Sarcoid myocarditis
D86.86	Sarcoid arthropathy
D86.87	Sarcoid myositis
D86.89	Sarcoidosis of other sites
D86.9	Sarcoidosis, unspecified
H20.041	Secondary noninfectious iridocyclitis, right eye
H20.042	Secondary noninfectious iridocyclitis, left eye
H20.043	Secondary noninfectious iridocyclitis, bilateral
H20.049	Secondary noninfectious iridocyclitis, unspecified eye

ICD-10 Diagnosis	Description
H44.131	Sympathetic uveitis, right eye
H44.132	Sympathetic uveitis, left eye
H44.133	Sympathetic uveitis, bilateral
H44.139	Sympathetic uveitis, unspecified eye
I30.8	Other forms of acute pericarditis
I30.9	Acute pericarditis, unspecified
I40.8	Other acute myocarditis
I40.9	Acute myocarditis, unspecified
I50.9	Heart failure, unspecified
J70.2	Acute drug-induced interstitial lung disorders
J70.4	Drug-induced interstitial lung disorders, unspecified
K31.6	Fistula of stomach and duodenum
K50.00	Crohn's disease of small intestine without complications
K50.011	Crohn's disease of small intestine with rectal bleeding
K50.012	Crohn's disease of small intestine with intestinal obstruction
K50.013	Crohn's disease of small intestine with fistula
K50.014	Crohn's disease of small intestine with abscess
K50.018	Crohn's disease of small intestine with other complication
K50.019	Crohn's disease of small intestine with unspecified complications
K50.10	Crohn's disease of large intestine without complications
K50.111	Crohn's disease of large intestine with rectal bleeding
K50.112	Crohn's disease of large intestine with intestinal obstruction
K50.113	Crohn's disease of large intestine with fistula
K50.114	Crohn's disease of large intestine with abscess
K50.118	Crohn's disease of large intestine with other complication
K50.119	Crohn's disease of large intestine with unspecified complications
K50.80	Crohn's disease of both small and large intestine without complications
K50.811	Crohn's disease of both small and large intestine with rectal bleeding
K50.812	Crohn's disease of both small and large intestine with intestinal obstruction
K50.813	Crohn's disease of both small and large intestine with fistula
K50.814	Crohn's disease of both small and large intestine with abscess
K50.818	Crohn's disease of both small and large intestine with other complication
K50.819	Crohn's disease of both small and large intestine with unspecified complications
K50.90	Crohn's disease, unspecified, without complications
K50.911	Crohn's disease, unspecified, with rectal bleeding
K50.912	Crohn's disease, unspecified, with intestinal obstruction
K50.913	Crohn's disease, unspecified, with fistula
K50.914	Crohn's disease, unspecified, with abscess
K50.918	Crohn's disease, unspecified, with other complication
K50.919	Crohn's disease, unspecified, with unspecified complications
K51.00	Ulcerative (chronic) pancolitis without complications
K51.011	Ulcerative (chronic) pancolitis with rectal bleeding
K51.012	Ulcerative (chronic) pancolitis with intestinal obstruction
K51.013	Ulcerative (chronic) pancolitis with fistula
K51.014	Ulcerative (chronic) pancolitis with abscess
K51.018	Ulcerative (chronic) pancolitis with other complication
K51.019	Ulcerative (chronic) pancolitis with unspecified complications

ICD-10 Diagnosis	Description
K51.20	Ulcerative (chronic) proctitis without complications
K51.211	Ulcerative (chronic) proctitis with rectal bleeding
K51.212	Ulcerative (chronic) proctitis with intestinal obstruction
K51.213	Ulcerative (chronic) proctitis with fistula
K51.214	Ulcerative (chronic) proctitis with abscess
K51.218	Ulcerative (chronic) proctitis with other complication
K51.219	Ulcerative (chronic) proctitis with unspecified complications
K51.30	Ulcerative (chronic) rectosigmoiditis without complications
K51.311	Ulcerative (chronic) rectosigmoiditis with rectal bleeding
K51.312	Ulcerative (chronic) rectosigmoiditis with intestinal obstruction
K51.313	Ulcerative (chronic) rectosigmoiditis with fistula
K51.314	Ulcerative (chronic) rectosigmoiditis with abscess
K51.318	Ulcerative (chronic) rectosigmoiditis with other complication
K51.319	Ulcerative (chronic) rectosigmoiditis with unspecified complications
K51.40	Inflammatory polyps of colon without complications
K51.411	Inflammatory polyps of colon with rectal bleeding
K51.412	Inflammatory polyps of colon with intestinal obstruction
K51.413	Inflammatory polyps of colon with fistula
K51.414	Inflammatory polyps of colon with abscess
K51.418	Inflammatory polyps of colon with other complication
K51.419	Inflammatory polyps of colon with unspecified complications
K51.50	Left sided colitis without complications
K51.511	Left sided colitis with rectal bleeding
K51.512	Left sided colitis with intestinal obstruction
K51.513	Left sided colitis with fistula
K51.514	Left sided colitis with abscess
K51.518	Left sided colitis with other complication
K51.519	Left sided colitis with unspecified complications
K51.80	Other ulcerative colitis without complications
K51.811	Other ulcerative colitis with rectal bleeding
K51.812	Other ulcerative colitis with intestinal obstruction
K51.813	Other ulcerative colitis with fistula
K51.814	Other ulcerative colitis with abscess
K51.818	Other ulcerative colitis with other complication
K51.819	Other ulcerative colitis with unspecified complications
K51.90	Ulcerative colitis, unspecified, without complications
K51.911	Ulcerative colitis, unspecified with rectal bleeding
K51.912	Ulcerative colitis, unspecified with intestinal obstruction
K51.913	Ulcerative colitis, unspecified with fistula
K51.914	Ulcerative colitis, unspecified with abscess
K51.918	Ulcerative colitis, unspecified with other complication
K51.919	Ulcerative colitis, unspecified with unspecified complications
K52.1	Toxic gastroenteritis and colitis
K60.3	Anal fistula
K60.4	Rectal fistula
K60.5	Anorectal fistula
K63.2	Fistula of intestine

ICD-10 Diagnosis	Description
L40.0	Psoriasis vulgaris
L40.1	Generalized pustular psoriasis
L40.2	Acrodermatitis continua
L40.3	Pustulosis palmaris et plantaris
L40.4	Guttate psoriasis
L40.50	Arthropathic psoriasis, unspecified
L40.51	Distal interphalangeal psoriatic arthropathy
L40.52	Psoriatic arthritis mutilans
L40.53	Psoriatic spondylitis
L40.54	Psoriatic juvenile arthropathy
L40.59	Other psoriatic arthropathy
L40.8	Other psoriasis
L40.9	Psoriasis, unspecified
M05.00	Felty's syndrome, unspecified site
M05.011	Felty's syndrome, right shoulder
M05.012	Felty's syndrome, left shoulder
M05.019	Felty's syndrome, unspecified shoulder
M05.021	Felty's syndrome, right elbow
M05.022	Felty's syndrome, left elbow
M05.029	Felty's syndrome, unspecified elbow
M05.031	Felty's syndrome, right wrist
M05.032	Felty's syndrome, left wrist
M05.039	Felty's syndrome, unspecified wrist
M05.041	Felty's syndrome, right hand
M05.042	Felty's syndrome, left hand
M05.049	Felty's syndrome, unspecified hand
M05.051	Felty's syndrome, right hip
M05.052	Felty's syndrome, left hip
M05.059	Felty's syndrome, unspecified hip
M05.061	Felty's syndrome, right knee
M05.062	Felty's syndrome, left knee
M05.069	Felty's syndrome, unspecified knee
M05.071	Felty's syndrome, right ankle and foot
M05.072	Felty's syndrome, left ankle and foot
M05.079	Felty's syndrome, unspecified ankle and foot
M05.09	Felty's syndrome, multiple sites
M05.20	Rheumatoid vasculitis with rheumatoid arthritis of unspecified site
M05.211	Rheumatoid vasculitis with rheumatoid arthritis of right shoulder
M05.212	Rheumatoid vasculitis with rheumatoid arthritis of left shoulder
M05.219	Rheumatoid vasculitis with rheumatoid arthritis of unspecified shoulder
M05.221	Rheumatoid vasculitis with rheumatoid arthritis of right elbow
M05.222	Rheumatoid vasculitis with rheumatoid arthritis of left elbow
M05.229	Rheumatoid vasculitis with rheumatoid arthritis of unspecified elbow
M05.231	Rheumatoid vasculitis with rheumatoid arthritis of right wrist
M05.232	Rheumatoid vasculitis with rheumatoid arthritis of left wrist
M05.239	Rheumatoid vasculitis with rheumatoid arthritis of unspecified wrist
M05.241	Rheumatoid vasculitis with rheumatoid arthritis of right hand

ICD-10 Diagnosis	Description
M05.242	Rheumatoid vasculitis with rheumatoid arthritis of left hand
M05.249	Rheumatoid vasculitis with rheumatoid arthritis of unspecified hand
M05.251	Rheumatoid vasculitis with rheumatoid arthritis of right hip
M05.252	Rheumatoid vasculitis with rheumatoid arthritis of left hip
M05.259	Rheumatoid vasculitis with rheumatoid arthritis of unspecified hip
M05.261	Rheumatoid vasculitis with rheumatoid arthritis of right knee
M05.262	Rheumatoid vasculitis with rheumatoid arthritis of left knee
M05.269	Rheumatoid vasculitis with rheumatoid arthritis of unspecified knee
M05.271	Rheumatoid vasculitis with rheumatoid arthritis of right ankle and foot
M05.272	Rheumatoid vasculitis with rheumatoid arthritis of left ankle and foot
M05.279	Rheumatoid vasculitis with rheumatoid arthritis of unspecified ankle and foot
M05.29	Rheumatoid vasculitis with rheumatoid arthritis of multiple sites
M05.30	Rheumatoid heart disease with rheumatoid arthritis of unspecified site
M05.311	Rheumatoid heart disease with rheumatoid arthritis of right shoulder
M05.312	Rheumatoid heart disease with rheumatoid arthritis of left shoulder
M05.319	Rheumatoid heart disease with rheumatoid arthritis of unspecified shoulder
M05.321	Rheumatoid heart disease with rheumatoid arthritis of right elbow
M05.322	Rheumatoid heart disease with rheumatoid arthritis of left elbow
M05.329	Rheumatoid heart disease with rheumatoid arthritis of unspecified elbow
M05.331	Rheumatoid heart disease with rheumatoid arthritis of right wrist
M05.332	Rheumatoid heart disease with rheumatoid arthritis of left wrist
M05.339	Rheumatoid heart disease with rheumatoid arthritis of unspecified wrist
M05.341	Rheumatoid heart disease with rheumatoid arthritis of right hand
M05.342	Rheumatoid heart disease with rheumatoid arthritis of left hand
M05.349	Rheumatoid heart disease with rheumatoid arthritis of unspecified hand
M05.351	Rheumatoid heart disease with rheumatoid arthritis of right hip
M05.352	Rheumatoid heart disease with rheumatoid arthritis of left hip
M05.359	Rheumatoid heart disease with rheumatoid arthritis of unspecified hip
M05.361	Rheumatoid heart disease with rheumatoid arthritis of right knee
M05.362	Rheumatoid heart disease with rheumatoid arthritis of left knee
M05.369	Rheumatoid heart disease with rheumatoid arthritis of unspecified knee
M05.371	Rheumatoid heart disease with rheumatoid arthritis of right ankle and foot
M05.372	Rheumatoid heart disease with rheumatoid arthritis of left ankle and foot
M05.379	Rheumatoid heart disease with rheumatoid arthritis of unspecified ankle and foot
M05.39	Rheumatoid heart disease with rheumatoid arthritis of multiple sites
M05.40	Rheumatoid myopathy with rheumatoid arthritis of unspecified site
M05.411	Rheumatoid myopathy with rheumatoid arthritis of right shoulder
M05.412	Rheumatoid myopathy with rheumatoid arthritis of left shoulder
M05.419	Rheumatoid myopathy with rheumatoid arthritis of unspecified shoulder
M05.421	Rheumatoid myopathy with rheumatoid arthritis of right elbow
M05.422	Rheumatoid myopathy with rheumatoid arthritis of left elbow
M05.429	Rheumatoid myopathy with rheumatoid arthritis of unspecified elbow
M05.431	Rheumatoid myopathy with rheumatoid arthritis of right wrist
M05.432	Rheumatoid myopathy with rheumatoid arthritis of left wrist
M05.439	Rheumatoid myopathy with rheumatoid arthritis of unspecified wrist
M05.441	Rheumatoid myopathy with rheumatoid arthritis of right hand
M05.442	Rheumatoid myopathy with rheumatoid arthritis of left hand

ICD-10 Diagnosis	Description
M05.449	Rheumatoid myopathy with rheumatoid arthritis of unspecified hand
M05.451	Rheumatoid myopathy with rheumatoid arthritis of right hip
M05.452	Rheumatoid myopathy with rheumatoid arthritis of left hip
M05.459	Rheumatoid myopathy with rheumatoid arthritis of unspecified hip
M05.461	Rheumatoid myopathy with rheumatoid arthritis of right knee
M05.462	Rheumatoid myopathy with rheumatoid arthritis of left knee
M05.469	Rheumatoid myopathy with rheumatoid arthritis of unspecified knee
M05.471	Rheumatoid myopathy with rheumatoid arthritis of right ankle and foot
M05.472	Rheumatoid myopathy with rheumatoid arthritis of left ankle and foot
M05.479	Rheumatoid myopathy with rheumatoid arthritis of unspecified ankle and foot
M05.49	Rheumatoid myopathy with rheumatoid arthritis of multiple sites
M05.50	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified site
M05.511	Rheumatoid polyneuropathy with rheumatoid arthritis of right shoulder
M05.512	Rheumatoid polyneuropathy with rheumatoid arthritis of left shoulder
M05.519	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified shoulder
M05.521	Rheumatoid polyneuropathy with rheumatoid arthritis of right elbow
M05.522	Rheumatoid polyneuropathy with rheumatoid arthritis of left elbow
M05.529	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified elbow
M05.531	Rheumatoid polyneuropathy with rheumatoid arthritis of right wrist
M05.532	Rheumatoid polyneuropathy with rheumatoid arthritis of left wrist
M05.539	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified wrist
M05.541	Rheumatoid polyneuropathy with rheumatoid arthritis of right hand
M05.542	Rheumatoid polyneuropathy with rheumatoid arthritis of left hand
M05.549	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified hand
M05.551	Rheumatoid polyneuropathy with rheumatoid arthritis of right hip
M05.552	Rheumatoid polyneuropathy with rheumatoid arthritis of left hip
M05.559	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified hip
M05.561	Rheumatoid polyneuropathy with rheumatoid arthritis of right knee
M05.562	Rheumatoid polyneuropathy with rheumatoid arthritis of left knee
M05.569	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified knee
M05.571	Rheumatoid polyneuropathy with rheumatoid arthritis of right ankle and foot
M05.572	Rheumatoid polyneuropathy with rheumatoid arthritis of left ankle and foot
M05.579	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified ankle and foot
M05.59	Rheumatoid polyneuropathy with rheumatoid arthritis of multiple sites
M05.60	Rheumatoid arthritis of unspecified site with involvement of other organs and systems
M05.611	Rheumatoid arthritis of right shoulder with involvement of other organs and systems
M05.612	Rheumatoid arthritis of left shoulder with involvement of other organs and systems
M05.619	Rheumatoid arthritis of unspecified shoulder with involvement of other organs and systems
M05.621	Rheumatoid arthritis of right elbow with involvement of other organs and systems
M05.622	Rheumatoid arthritis of left elbow with involvement of other organs and systems
M05.629	Rheumatoid arthritis of unspecified elbow with involvement of other organs and systems
M05.631	Rheumatoid arthritis of right wrist with involvement of other organs and systems
M05.632	Rheumatoid arthritis of left wrist with involvement of other organs and systems
M05.639	Rheumatoid arthritis of unspecified wrist with involvement of other organs and systems

ICD-10 Diagnosis	Description
M05.641	Rheumatoid arthritis of right hand with involvement of other organs and systems
M05.642	Rheumatoid arthritis of left hand with involvement of other organs and systems
M05.649	Rheumatoid arthritis of unspecified hand with involvement of other organs and systems
M05.651	Rheumatoid arthritis of right hip with involvement of other organs and systems
M05.652	Rheumatoid arthritis of left hip with involvement of other organs and systems
M05.659	Rheumatoid arthritis of unspecified hip with involvement of other organs and systems
M05.661	Rheumatoid arthritis of right knee with involvement of other organs and systems
M05.662	Rheumatoid arthritis of left knee with involvement of other organs and systems
M05.669	Rheumatoid arthritis of unspecified knee with involvement of other organs and systems
M05.671	Rheumatoid arthritis of right ankle and foot with involvement of other organs and systems
M05.672	Rheumatoid arthritis of left ankle and foot with involvement of other organs and systems
M05.679	Rheumatoid arthritis of unspecified ankle and foot with involvement of other organs and systems
M05.69	Rheumatoid arthritis of multiple sites with involvement of other organs and systems
M05.70	Rheumatoid arthritis with rheumatoid factor of unspecified site without organ or systems involvement
M05.711	Rheumatoid arthritis with rheumatoid factor of right shoulder without organ or systems involvement
M05.712	Rheumatoid arthritis with rheumatoid factor of left shoulder without organ or systems involvement
M05.719	Rheumatoid arthritis with rheumatoid factor of unspecified shoulder without organ or systems involvement
M05.721	Rheumatoid arthritis with rheumatoid factor of right elbow without organ or systems involvement
M05.722	Rheumatoid arthritis with rheumatoid factor of left elbow without organ or systems involvement
M05.729	Rheumatoid arthritis with rheumatoid factor of unspecified elbow without organ or systems involvement
M05.731	Rheumatoid arthritis with rheumatoid factor of right wrist without organ or systems involvement
M05.732	Rheumatoid arthritis with rheumatoid factor of left wrist without organ or systems involvement
M05.739	Rheumatoid arthritis with rheumatoid factor of unspecified wrist without organ or systems involvement
M05.741	Rheumatoid arthritis with rheumatoid factor of right hand without organ or systems involvement
M05.742	Rheumatoid arthritis with rheumatoid factor of left hand without organ or systems involvement
M05.749	Rheumatoid arthritis with rheumatoid factor of unspecified hand without organ or systems involvement
M05.751	Rheumatoid arthritis with rheumatoid factor of right hip without organ or systems involvement
M05.752	Rheumatoid arthritis with rheumatoid factor of left hip without organ or systems involvement
M05.759	Rheumatoid arthritis with rheumatoid factor of unspecified hip without organ or systems involvement
M05.761	Rheumatoid arthritis with rheumatoid factor of right knee without organ or systems involvement

ICD-10 Diagnosis	Description
M05.762	Rheumatoid arthritis with rheumatoid factor of left knee without organ or systems involvement
M05.769	Rheumatoid arthritis with rheumatoid factor of unspecified knee without organ or systems involvement
M05.771	Rheumatoid arthritis with rheumatoid factor of right ankle and foot without organ or systems involvement
M05.772	Rheumatoid arthritis with rheumatoid factor of left ankle and foot without organ or systems involvement
M05.779	Rheumatoid arthritis with rheumatoid factor of unspecified ankle and foot without organ or systems involvement
M05.79	Rheumatoid arthritis with rheumatoid factor of multiple sites without organ or systems involvement
M05.80	Other rheumatoid arthritis with rheumatoid factor of unspecified site
M05.811	Other rheumatoid arthritis with rheumatoid factor of right shoulder
M05.812	Other rheumatoid arthritis with rheumatoid factor of left shoulder
M05.819	Other rheumatoid arthritis with rheumatoid factor of unspecified shoulder
M05.821	Other rheumatoid arthritis with rheumatoid factor of right elbow
M05.822	Other rheumatoid arthritis with rheumatoid factor of left elbow
M05.829	Other rheumatoid arthritis with rheumatoid factor of unspecified elbow
M05.831	Other rheumatoid arthritis with rheumatoid factor of right wrist
M05.832	Other rheumatoid arthritis with rheumatoid factor of left wrist
M05.839	Other rheumatoid arthritis with rheumatoid factor of unspecified wrist
M05.841	Other rheumatoid arthritis with rheumatoid factor of right hand
M05.842	Other rheumatoid arthritis with rheumatoid factor of left hand
M05.849	Other rheumatoid arthritis with rheumatoid factor of unspecified hand
M05.851	Other rheumatoid arthritis with rheumatoid factor of right hip
M05.852	Other rheumatoid arthritis with rheumatoid factor of left hip
M05.859	Other rheumatoid arthritis with rheumatoid factor of unspecified hip
M05.861	Other rheumatoid arthritis with rheumatoid factor of right knee
M05.862	Other rheumatoid arthritis with rheumatoid factor of left knee
M05.869	Other rheumatoid arthritis with rheumatoid factor of unspecified knee
M05.871	Other rheumatoid arthritis with rheumatoid factor of right ankle and foot
M05.872	Other rheumatoid arthritis with rheumatoid factor of left ankle and foot
M05.879	Other rheumatoid arthritis with rheumatoid factor of unspecified ankle and foot
M05.89	Other rheumatoid arthritis with rheumatoid factor of multiple sites
M05.9	Rheumatoid arthritis with rheumatoid factor, unspecified
M06.00	Rheumatoid arthritis without rheumatoid factor, unspecified site
M06.011	Rheumatoid arthritis without rheumatoid factor, right shoulder
M06.012	Rheumatoid arthritis without rheumatoid factor, left shoulder
M06.019	Rheumatoid arthritis without rheumatoid factor, unspecified shoulder
M06.021	Rheumatoid arthritis without rheumatoid factor, right elbow
M06.022	Rheumatoid arthritis without rheumatoid factor, left elbow
M06.029	Rheumatoid arthritis without rheumatoid factor, unspecified elbow
M06.031	Rheumatoid arthritis without rheumatoid factor, right wrist
M06.032	Rheumatoid arthritis without rheumatoid factor, left wrist
M06.039	Rheumatoid arthritis without rheumatoid factor, unspecified wrist
M06.041	Rheumatoid arthritis without rheumatoid factor, right hand
M06.042	Rheumatoid arthritis without rheumatoid factor, left hand
M06.049	Rheumatoid arthritis without rheumatoid factor, unspecified hand

ICD-10 Diagnosis	Description
M06.051	Rheumatoid arthritis without rheumatoid factor, right hip
M06.052	Rheumatoid arthritis without rheumatoid factor, left hip
M06.059	Rheumatoid arthritis without rheumatoid factor, unspecified hip
M06.061	Rheumatoid arthritis without rheumatoid factor, right knee
M06.062	Rheumatoid arthritis without rheumatoid factor, left knee
M06.069	Rheumatoid arthritis without rheumatoid factor, unspecified knee
M06.071	Rheumatoid arthritis without rheumatoid factor, right ankle and foot
M06.072	Rheumatoid arthritis without rheumatoid factor, left ankle and foot
M06.079	Rheumatoid arthritis without rheumatoid factor, unspecified ankle and foot
M06.08	Rheumatoid arthritis without rheumatoid factor, vertebrae
M06.09	Rheumatoid arthritis without rheumatoid factor, multiple sites
M06.1	Adult-onset Still's disease
M06.20	Rheumatoid bursitis, unspecified site
M06.211	Rheumatoid bursitis, right shoulder
M06.212	Rheumatoid bursitis, left shoulder
M06.219	Rheumatoid bursitis, unspecified shoulder
M06.221	Rheumatoid bursitis, right elbow
M06.222	Rheumatoid bursitis, left elbow
M06.229	Rheumatoid bursitis, unspecified elbow
M06.231	Rheumatoid bursitis, right wrist
M06.232	Rheumatoid bursitis, left wrist
M06.239	Rheumatoid bursitis, unspecified wrist
M06.241	Rheumatoid bursitis, right hand
M06.242	Rheumatoid bursitis, left hand
M06.249	Rheumatoid bursitis, unspecified hand
M06.251	Rheumatoid bursitis, right hip
M06.252	Rheumatoid bursitis, left hip
M06.259	Rheumatoid bursitis, unspecified hip
M06.261	Rheumatoid bursitis, right knee
M06.262	Rheumatoid bursitis, left knee
M06.269	Rheumatoid bursitis, unspecified knee
M06.271	Rheumatoid bursitis, right ankle and foot
M06.272	Rheumatoid bursitis, left ankle and foot
M06.279	Rheumatoid bursitis, unspecified ankle and foot
M06.28	Rheumatoid bursitis, vertebrae
M06.29	Rheumatoid bursitis, multiple sites
M06.30	Rheumatoid nodule, unspecified site
M06.311	Rheumatoid nodule, right shoulder
M06.312	Rheumatoid nodule, left shoulder
M06.319	Rheumatoid nodule, unspecified shoulder
M06.321	Rheumatoid nodule, right elbow
M06.322	Rheumatoid nodule, left elbow
M06.329	Rheumatoid nodule, unspecified elbow
M06.331	Rheumatoid nodule, right wrist
M06.332	Rheumatoid nodule, left wrist
M06.339	Rheumatoid nodule, unspecified wrist
M06.341	Rheumatoid nodule, right hand

ICD-10 Diagnosis	Description
M06.342	Rheumatoid nodule, left hand
M06.349	Rheumatoid nodule, unspecified hand
M06.351	Rheumatoid nodule, right hip
M06.352	Rheumatoid nodule, left hip
M06.359	Rheumatoid nodule, unspecified hip
M06.361	Rheumatoid nodule, right knee
M06.362	Rheumatoid nodule, left knee
M06.369	Rheumatoid nodule, unspecified knee
M06.371	Rheumatoid nodule, right ankle and foot
M06.372	Rheumatoid nodule, left ankle and foot
M06.379	Rheumatoid nodule, unspecified ankle and foot
M06.38	Rheumatoid nodule, vertebrae
M06.39	Rheumatoid nodule, multiple sites
M06.4	Inflammatory polyarthropathy
M06.80	Other specified rheumatoid arthritis, unspecified site
M06.811	Other specified rheumatoid arthritis, right shoulder
M06.812	Other specified rheumatoid arthritis, left shoulder
M06.819	Other specified rheumatoid arthritis, unspecified shoulder
M06.821	Other specified rheumatoid arthritis, right elbow
M06.822	Other specified rheumatoid arthritis, left elbow
M06.829	Other specified rheumatoid arthritis, unspecified elbow
M06.831	Other specified rheumatoid arthritis, right wrist
M06.832	Other specified rheumatoid arthritis, left wrist
M06.839	Other specified rheumatoid arthritis, unspecified wrist
M06.841	Other specified rheumatoid arthritis, right hand
M06.842	Other specified rheumatoid arthritis, left hand
M06.849	Other specified rheumatoid arthritis, unspecified hand
M06.851	Other specified rheumatoid arthritis, right hip
M06.852	Other specified rheumatoid arthritis, left hip
M06.859	Other specified rheumatoid arthritis, unspecified hip
M06.861	Other specified rheumatoid arthritis, right knee
M06.862	Other specified rheumatoid arthritis, left knee
M06.869	Other specified rheumatoid arthritis, unspecified knee
M06.871	Other specified rheumatoid arthritis, right ankle and foot
M06.872	Other specified rheumatoid arthritis, left ankle and foot
M06.879	Other specified rheumatoid arthritis, unspecified ankle and foot
M06.88	Other specified rheumatoid arthritis, vertebrae
M06.89	Other specified rheumatoid arthritis, multiple sites
M06.9	Rheumatoid arthritis, unspecified
M08.1	Juvenile ankylosing spondylitis
M45.0	Ankylosing spondylitis of multiple sites in spine
M45.1	Ankylosing spondylitis of occipito-atlanto-axial region
M45.2	Ankylosing spondylitis of cervical region
M45.3	Ankylosing spondylitis of cervicothoracic region
M45.4	Ankylosing spondylitis of thoracic region
M45.5	Ankylosing spondylitis of thoracolumbar region
M45.6	Ankylosing spondylitis lumbar region

ICD-10 Diagnosis	Description
M45.7	Ankylosing spondylitis of lumbosacral region
M45.8	Ankylosing spondylitis sacral and sacrococcygeal region
M45.9	Ankylosing spondylitis of unspecified sites in spine
M48.8X1	Other specified spondylopathies, occipito-atlanto-axial region
M48.8X2	Other specified spondylopathies, cervical region
M48.8X3	Other specified spondylopathies, cervicothoracic region
M48.8X4	Other specified spondylopathies, thoracic region
M48.8X5	Other specified spondylopathies, thoracolumbar region
M48.8X6	Other specified spondylopathies, lumbar region
M48.8X7	Other specified spondylopathies, lumbosacral region
M48.8X8	Other specified spondylopathies, sacral and sacrococcygeal region
M48.8X9	Other specified spondylopathies, site unspecified
N17.8	Other acute kidney failure
N17.9	Acute kidney failure, unspecified
N82.2	Fistula of vagina to small intestine
N82.3	Fistula of vagina to large intestine
N82.4	Other female intestinal-genital tract fistulae
R19.7	Diarrhea, unspecified

BACKGROUND

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

BENEFIT CONSIDERATIONS

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 the Administrative Policies titled 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 the Administrative Policy titled Acquired Rare Disease Drug Therapy Exception Process.

CLINICAL EVIDENCE

Proven

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 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 identity 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

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 disease[29-30], myelodysplastic syndromes[37], undifferentiated spondyloarthropathy[35], Reiter's syndrome[19], 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 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®] 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 2018 ACG Practice Guideline support the use of infliximab for treatment and maintenance of patients with moderate to severely active Crohn's disease which is resistant or refractory to corticosteroids, thiopurines or methotrexate In addition, they state anti-TNF agents can be considered to treat severely active Crohn's disease.[64]

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). Additionally, the American College of Rheumatology has provided recommendations for the treatment of ankylosing spondylitis. 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.[8,65]

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.[34,66]

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 (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.

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

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.

Avsola (infliximab-axxq), Inflectra (infliximab-dyyb) and Renflexis (infliximab-abda) are biosimilar* to Remicade (infliximab). Avsola, Inflectra and Renflexis are tumor necrosis factor (TNF) blockers indicated for:[57-60, 62]

- **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 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.

Reference Product	Biosimilar Product
Remicade	Avsola, Inflectra, Ixifi, Renflexis

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]

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. [*2019D0004AB*]

1. Remicade [prescribing information]. Horsham, PA: Janssen Biotech Inc.; June 2018.
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, 23rd Edition. Infliximab. Accessed on February 15, 2019.
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 (TNFα) 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 Behcet 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 antiTNFalpha 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 spondyloarthropathy 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, Lilienthal 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 spondyloarthropathy: response to anti-TNF therapy. *J Gastroenterol.* 2003;38(10):1000-4.

50. Rosi YL, Lowe L, Kang S. Treatment of hidradenitis 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 hidradenitis 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; October 2018

57. Inflectra [prescribing information]. New York, NY: Pfizer; July 2018.

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; November 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.

64. Lichtenstein GR, Loftus EV, Isaacs KL, Regueiro MD, Gerson LB, Sands BE. American College of Gastroenterology Practice Guidelines. Management of Crohn's Disease in Adults. *Am J Gastroenterol*. 2018 Apr;113(4):481-517.

65. Ward MM, Deodhar A, Akl EA, Lui A, et al. American College of Rheumatology/Spondylitis Association of America, Spondyloarthritis Research and Treatment Network 2015 Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis. Arthritis Rheumatol. 2016 Feb;68(2):282-98.

66. Ringold S, Weiss PF, Beukelman T, DeWitt EM et al. 2013 update of the 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: recommendations for the medical therapy of children with systemic juvenile idiopathic arthritis and tuberculosis screening among children receiving biologic medications. Arthritis Rheum. 2013 Oct;65(10):2499-512.

67. NCCN Clinical Practice Guidelines in Oncology® (NCCN Guidelines®). Management of Immunotherapy-Related Toxicities. Version 2.2019. Available at www.nccn.org. Accessed on April 10, 2019.

68. Avsola [prescribing information]. Thousand Oaks, CA: Amgen Inc.; December 2019.

POLICY HISTORY/REVISION INFORMATION

Date	Action/Description

02/01/2020	**Title Change**
	• Previously titled *Infliximab (Remicade®, Inflectra™, Renflexis™)*
	Conditions of Coverage
	• Added language to indicate precertification is not required, however it is strongly recommended for **Avsola**
	  ○ While no penalty will be imposed for failure to request a pre-service review, if one is not requested, a medical necessity review will be conducted post-service to determine coverage
	  ○ It is the referring physician's responsibility to provide medical documentation to demonstrate clinical necessity for the medication
	  ○ Beginning **May 1, 2020**, precertification **will** be required
	Coverage Rationale
	• Revised list of applicable infliximab products; added Avsola™ (infliximab-axxq)
	• Added language to indicate:
	  ○ Avsola (infliximab-axxq) has been added to the Review at Launch program and some members may not be eligible for coverage of this medication at this time; refer to the Medical Benefit Drug Policy titled *Review at Launch for New to Market Medications* for additional details
	Preferred Product: Medical Necessity Plans
	  ○ Coverage for Avsola™ (infliximab-axxq) will be provided contingent on the criteria in this section and the coverage criteria in the *Diagnosis-Specific Criteria* section [of the policy]
	  ○ In order to continue coverage, members already on Avsola will be required to change therapy to Inflectra or Remicade unless they meet the criteria in [the *Preferred Product Criteria*] section [of the policy]
	  ○ Treatment with Avsola is medically necessary for the indications specified in the policy when both of the [*Preferred Product Criteria* listed in the policy] are met
	• Replaced Preferred Product criterion requiring:
	  ○ "History of a trial of at least 14 weeks of Remicade and Inflectra resulting in minimal clinical response to therapy and residual disease activity" with "history of a trial of at least 14 weeks of *both* Inflectra and 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 [a non-preferred] infliximab biosimilar product, than experienced with Remicade ***or*** Inflectra" with "physician attests that in their clinical opinion, the clinical response would be expected to be superior with [a non-preferred] infliximab biosimilar product, than experienced with Inflectra ***and*** Remicade"
	  ○ "Patient has not developed neutralizing antibodies to any infliximab *biosimilar* product that has led to an attenuation of efficacy of therapy" with "patient has not developed neutralizing antibodies to any infliximab product that has led to an attenuation of efficacy of therapy"
	Applicable Codes
	• Added HCPCS codes J3490 and J3590
	Supporting Information
	• Updated *FDA* and *References* sections to reflect the most current information
	• Archived previous policy version PHARMACY 067.39 T2

INSTRUCTIONS FOR USE

This Clinical Policy provides assistance in interpreting UnitedHealthcare Oxford standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare Oxford reserves the right 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. Unless otherwise stated, Oxford policies do not apply to Medicare Advantage members.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. UnitedHealthcare Oxford Clinical Policies 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.