EXPRESS SCRIPTS®

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Infliximab Products (Inflectra/Remicade/Renflexis)

- Inflectra™ (infliximab-dyyb for injection, for intravenous use – Hospira/Pfizer)
- Remicade® (infliximab for intravenous infusion – Janssen Biotech, Inc.)
- Renflexis® (infliximab-abda intravenous infusion – Samsung Bioepis/Merck)

TAC APPROVAL DATE: 07/12/2017; selected revision 07/26/2017 and 10/18/2017

OVERVIEW

Infliximab is a chimeric (murine-human) Immunoglobulin (Ig) G1κ monoclonal antibody produced by recombinant DNA technology that binds specifically with human tumor necrosis factor-alpha (TNF-α).[1] The recommended dose of infliximab is weight-based and varies slightly by indication. Dosing increase, interval shortening, or changing to another therapy is generally recommended for attenuation of response.[2]

Inflectra and Renflexis were approved as biosimilar to Remicade, indicating no clinically meaningful differences in safety and effectiveness and the same mechanism of action, route of administration, dosage form, and strength as Remicade.[117] However, minor differences in clinically inactive components are allowed. At this time, Inflectra and Renflexis have only demonstrated biosimilarity, not interchangeability.

Infliximab (Inflectra, Remicade, and Renflexis) is indicated for the following conditions:

1. in combination with methotrexate (MTX) for reducing signs and symptoms, inhibiting the progression of structural damage and improving physical function in patients with moderately to severely active RA;[1,3-6]
2. reducing the signs and symptoms and inducing and maintaining clinical remission in adult and pediatric patients ≥ 6 years of age with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy;[1,7-9]
3. reduction in the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adults with fistulizing Crohn's disease;[1,10-11]
4. reducing signs and symptoms in adults with active ankylosing spondylitis (AS);[1,12]
5. reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage and improving physical function in adults with psoriatic arthritis (PsA);[1,13]
6. treatment of adults with chronic severe (i.e., extensive and/or disabling) plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are less appropriate;[1,14-16] AND
7. reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adults with moderately to severely active ulcerative colitis (UC) who have had an inadequate response to conventional therapy.[1,17]

In addition to the above indications, Remicade has marketing exclusivity and is also indicated for the following condition.[1] Although Inflectra and Renflexis do not share this indication, the prescribing information notes that pediatric assessment demonstrated safety and efficacy in this indication.[117]

1. reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients ≥ 6 years of age with moderately to severely active UC who have had an inadequate response to conventional therapy.[1]

Disease Overview

Increased levels of TNF are found in the joints of patients with rheumatoid arthritis (RA) and the stools of patients with Crohn's disease and correlate with elevated disease activity. TNF has an important role in both the pathologic inflammation and the joint destruction that are characteristic of RA. TNF is a naturally occurring cytokine that mediates inflammation and modulates cellular immune responses. Increased levels of TNF have been implicated in the pathology of inflammatory conditions such as psoriasis, psoriatic arthritis, inflammatory bowel disease, and rheumatoid arthritis (RA). Increased levels of TNF are found in the synovial fluid of patients with RA, JIA, AS, and PsA; TNF has an important role in both the pathologic inflammation and the joint destruction that are characteristic of this disease. In psoriasis, increased levels of TNF are found in the blood and skin lesions. Infliximab products binds to TNFα and inhibits binding of TNFα with its receptors.

Guidelines

TNFis feature prominently in guidelines for treatment of inflammatory conditions.[18-22,28-32,35-36,39-40,55,59,90] Guidelines from the American College of Rheumatology (ACR) [2015] have TNFis (e.g., Cimzia® [certolizumab pegol SC injection], etanercept SC products [e.g., Enbrel®], adalimumab SC products [e.g., Humira®], infliximab IV products [e.g., Remicade®, Renflexis, Inflectra], Simponi® [golimumab SC injection], Simponi Aria® [golimumab IV infusion]) and non-TNF biologics (i.e., Actemra® [tocilizumab IV infusion, tocilizumab SC injection], Orencia® [abatacept IV infusion, abatacept SC injection], rituximab IV products [e.g., Rituxan®]), administered with or without MTX, equally positioned as a recommended therapy following a trial of a csDMARD (e.g., MTX, leflunomide, hydroxychloroquine, sulfasalazine).[18] Other guidelines for inflammatory conditions (e.g., PsA [European Union Against Rheumatism; Group for Research and Assessment of Psoriasis and Psoriatic Arthritis {GRAPPA}] and spondylitis [AS and non-radiographic axial {nr-ax}SpA] {ACR and Spondylitis Association of America/Spondyloarthritis Research and Treatment Network}, inflammatory bowel disease [Crohn's disease, UC] {American Gastroenterological Association} also note the significant place in therapy for TNFis.[19-22,31-32,36-36,90]

Safety

Infliximab has Boxed Warnings concerning risks of serious infection and the risk of malignancy.[1] Prior to initiating therapy with infliximab, patients should be evaluated for active tuberculosis (TB) infection, and periodically during therapy patients should be assessed for latent TB infection. Patients should also be monitored for signs and symptoms of infection during and after treatment with infliximab, and if a serious infection or sepsis develops, infliximab should be discontinued. It is also recommended that patients treated with any TNF antagonist should be monitored for malignancies.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of infliximab. Because of the specialized skills required for evaluation and diagnosis of patients treated with infliximab as well as the monitoring required for adverse events and long-term efficacy, initial approval requires infliximab to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration listed below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of infliximab (e.g., Inflectra, Remicade, Renflexis) is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Rheumatoid Arthritis (RA)**: Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy: Approve for 3 months if the patient meets BOTH of the following criteria (i and ii):
     - **i.** The patient has tried ONE conventional synthetic disease-modifying antirheumatic drug (DMARD) for at least 3 months (e.g., methotrexate [oral or injectable], leflunomide, hydroxychloroquine, and sulfasalazine).
       NOTE: An exception to the requirement for a trial of one conventional synthetic DMARD can be made if the patient has already had a 3-month trial at least one biologic (e.g., Cimzia [certolizumab pegol SC injection], Enbrel [etanercept SC injection], Humira [adalimumab SC injection], Simponi/Aria [golimumab SC injection, golimumab IV infusion], Actemra [tocilizumab IV infusion, tocilizumab SC injection], Kevzara [sarilumab SC injection], Kineret [anakinra SC injection], Orencia [abatacept IV infusion, abatacept SC injection], and Rituxan [rituximab IV infusion]. These patients who have already tried a biologic for RA are not required to "step back" and try a conventional synthetic DMARD); AND
     - **ii.** Infliximab (Inflectra, Remicade, Renflexis) is prescribed by or in consultation with a rheumatologist.
   - **B)** Patients Currently Receiving Infliximab (e.g., Inflectra, Remicade, Renflexis): Approve for 3 years if the patient has had a response (e.g., less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths; improved laboratory values; reduced dosage of corticosteroids), as determined by the prescriber. The patient may not have a full response, but there should have been a recent or past response to infliximab.

   Guidelines from the American College of Rheumatology (ACR) [2015] have TNF inhibitors (e.g., Cimzia, Enbrel, Humira, infliximab, Simponi SC/Aria) and non-TNF biologics (i.e., Actemra, Orencia, Rituxan), administered with or without MTX, equally positioned as a recommended therapy following a trial of a conventional synthetic DMARD (e.g., MTX, leflunomide, hydroxychloroquine, sulfasalazine).[18]

2. **Ankylosing Spondylitis (AS):** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy: Approve for 3 months if prescribed by or in consultation with a rheumatologist.
   - **B)** Patients Currently Receiving Infliximab (e.g., Inflectra, Remicade, Renflexis): Approve for 3 years if the patient has had a response (e.g., decreased pain or stiffness, improved function or activities of daily living), as determined by the prescriber. The patient may not have a full response, but there should have been a recent or past response to infliximab.

   Guidelines for axial spondyloarthritis are available from the Assessment of SpondyloArthritis International Society (ASAS)/EULAR (2016).[116] The guidelines state that biologics (e.g., TNFis, Cosentyx) should be

considered in patients with persistently high disease activity despite traditional conventional treatments (e.g., nonpharmacological management, NSAIDs). For patients with primarily peripheral manifestations of axial spondylitis, local steroid injections and sulfasalazine may be considered as conventional treatment; however, these are not considered for patients who present primarily with axial disease. Furthermore, the guidelines state that patients with purely axial disease should not be treated with conventional synthetic DMARDs. Guidelines from the American College of Rheumatology (ACR) and the Spondyloarthritis Research and Treatment Network (SPARTAN) [2015] make recommendations for treatment of AS.[19] TNF inhibitors (e.g., Cimzia, Enbrel, Humira, infliximab, Simponi SC) are recommended for patients who have active disease despite treatment with an NSAID. There is not a preference for TNF inhibitor, except for in the cases of concomitant inflammatory bowel disease or recurrent iritis, when a monoclonal antibody (Humira, infliximab) is recommended over Enbrel. According to Assessments in Ankylosing Spondylitis international Society/European League Against Rheumatism (ASAS/EULAR) 2010 recommendations for ankylosing spondylitis, all patients should have an adequate trial of at least two nonsteroidal anti-inflammatory drugs (NSAIDs) for pain and stiffness, unless contraindicated.[20-21] Recommendations for other therapies before receiving a TNF blocker vary according to the manifestations of the disease, level of current symptoms, clinical findings, etc. According to these recommendations, patients with pure axial manifestations do not have to try traditional DMARDs before anti-TNF agents such as infliximab; patients with symptomatic peripheral arthritis should have an insufficient response to at least one local corticosteroid injection, if appropriate; patients with peripheral arthritis should normally have a trial of a DMARD, preferably sulfasalazine; and patients with enthesitis should try appropriate local therapy (e.g., corticosteroid injection in selected cases). In patients with AS, concomitant treatment with a nonbiologic DMARD does not add to the safety or efficacy with an anti-TNF inhibitor.[23]

3. Crohn's Disease in a Patient ≥ 6 Years of Age: Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy: Approve for 3 months if the patient meets the following criteria (i and ii):

i. The patient meets ONE of the following conditions (a, b, c, or d):

a) The patient has tried or is currently taking corticosteroids, or corticosteroids are contraindicated in this patient (Note: Examples of corticosteroids are prednisone, methylprednisolone); OR

b) The patient has tried one other agent for Crohn's disease (e.g., azathioprine, 6-mercaptopurine, or methotrexate [MTX]).
NOTE: A previous trial of a biologic (e.g., Cimzia [certolizumab pegol SC injection], Entyvio [vedolizumab IV infusion], Humira [adalimumab SC injection], or Stelara [ustekinumab IV infusion, ustekinumab SC injection]) also counts as a trial of one other agent for Crohn's disease; OR

c) The patient has enterocutaneous (perianal or abdominal) or rectovaginal fistulas; OR

d) The patient has had ileocolonic resection (to reduce the chance of Crohn's disease recurrence); AND

ii. Infliximab (e.g., Inflectra, Remicade, Renflexis) is prescribed by or in consultation with a gastroenterologist.

B) Patients Currently Receiving Infliximab (e.g., Inflectra, Remicade, Renflexis): Approve for 3 years if the patient has had a response, as determined by the prescriber. The patient may not have a full response, but there should have been a recent or past response to infliximab.

In addition to the approved indication, infliximab has also been shown to reduce the chance of recurrence of symptoms after surgery in patients with Crohn's disease.[24-27] In one study, patients

treated with Infliximab following illeocolonic resection of Crohn's disease noticed a significant decrease in Crohn's Disease Activity Index (CDAI) score at Month 2 ($P < 0.01$ compared with baseline); this decrease in CDAI was not found in study patients treated post-resection with mesalamine or azathioprine.[25] The American Gastroenterological Association (AGA) has guidelines for Crohn's disease (2013).[28] For induction therapy, TNF blockers are listed as a strong recommendation for patients with moderately severe CD (moderate-quality evidence). In the professional opinion of specialist physicians reviewing the data, we have adopted these criteria.

4. **Plaque Psoriasis:** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy: Approve for 3 months if the patient meets the following criteria (i, ii, and iii):
     - **i.** The patient is an adult greater than or equal to 18 years of age; AND
     - **ii.** The patient meets ONE of the following conditions (a or b):
       - **a)** The patient has tried at least at least one traditional systemic agent for psoriasis (e.g., methotrexate [MTX], cyclosporine, acitretin [Soriatane®, generics], or psoralen plus ultraviolet A light [PUVA]) for at least 3 months, unless intolerant.
         NOTE: An exception to the requirement for a trial of one traditional systemic agent for psoriasis can be made if the patient has already has a 3-month trial or previous intolerance to at least one biologic (e.g., Enbrel [etanercept for SC injection], Cosentyx [secukinumab for SC injection], Humira [adalimumab for SC injection], Stelara [ustekinumab for SC injection], or Taltz [ixekizumab for SC injection]). These patients who have already tried a biologic for psoriasis are not required to "step back" and try a traditional systemic agent for psoriasis); OR
       - **b)** The patient has a contraindication to methotrexate (MTX), as determined by the prescribing physician.
     - **iii.** Infliximab (e.g., Inflectra, Remicade, Renflexis) is prescribed by or in consultation with a dermatologist.
   - **B)** Patients Currently Receiving Infliximab (e.g., Inflectra, Remicade, Renflexis): Approve for 3 years if the patient has had a response, as determined by the prescriber. The patient may not have a full response, but there should have been a recent or past response to infliximab.

   Guidelines for treatment of plaque psoriasis recommend topical therapy for limited disease.[29-30] However, for patients with chronic plaque psoriasis that does not respond to topical therapies or patients with more extensive disease, systemic therapy may be used. The traditional systemic agents for plaque psoriasis are MTX, acitretin, and cyclosporine. A biologic agent such as infliximab is an option for patients who are candidates for phototherapy or systemic therapy, especially those who are intolerant of or unresponsive to traditional systemic agents. In the professional opinion of specialist physicians reviewing the data, we have adopted the criteria requirements for previous therapy.

5. **Psoriatic Arthritis (PsA):** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy: Approve for 3 months if prescribed by or in consultation with a rheumatologist or a dermatologist.
   - **B)** Patients Currently Receiving Infliximab (e.g., Inflectra, Remicade, Renflexis): Approve for 3 years if the patient has had a response (e.g., less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths; improvements in acute phase reactants [for example, C-reactive protein {CRP}]), as determined by the prescriber. The patient may not have a full response, but there should have been a recent or past response to infliximab.

In clinical trials, infliximab was effective in patients with active PsA despite therapy with a DMARD or NSAID. There are few well-controlled, prospective studies with adequate duration that have evaluated the efficacy of the oral DMARDs. Recommendations for the management of PsA have been developed by EULAR (2015) and the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) [2015].[31-32] According to EULAR, treatment is recommended based on clinical presentation.[31] In peripheral arthritis, a biologic (usually a TNF blocker) should be started if there is an inadequate response to at least one conventional synthetic DMARD. This recommendation is supported by the long-term experience and established safety/efficacy balance of TNF blockers vs. other biologics. In patients with enthesitis, dactylitis, or axial disease, the initial DMARD recommended are biologics; according to current practice a TNF blocker would be used. The guidelines note that comparison across trials is difficult because different outcomes were used. For enthesitis/dactylitis, the longest clinical experience is with TNF blockers. For axial disease, limited data exist for IL blockers. In patients who fail to respond to a biologic, switching to another biologic should be considered, including switching between TNF blockers. GRAPPA recommends TNF blockers for patients presenting with various manifestations of PsA (i.e., peripheral arthritis, axial disease, enthesitis, dactylitis, skin, and nail disease).[32]

6. Ulcerative Colitis in a Patient ≥ 6 Years of Age: Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy: Approve for 3 months if the patient meets the following criteria (i and ii):

i. The patient meets ONE of the following conditions (a or b):

a) Patient has had a 2-month trial of one systemic agent (e.g., 6-mercaptopurine, azathioprine, cyclosporine, tacrolimus, or a corticosteroid such as prednisone, methylprednisolone) or was intolerant to one of these agents for ulcerative colitis;
(NOTE: A previous trial of a biologic [e.g., Humira {adalimumab SC injection}, Simponi SC {golimumab SC injection} also counts as a trial of one systemic agent for UC); OR

b) The patient has pouchitis AND has tried therapy with an antibiotic (e.g., metronidazole, ciprofloxacin), probiotic, corticosteroid enema (for example, hydrocortisone enema [Cortenema®, generics]), or Rowasa® (mesalamine) enema; AND

ii. Infliximab (e.g., Inflectra, Remicade, Renflexis) is prescribed by or in consultation with a gastroenterologist.

B) Patients Currently Receiving Infliximab (e.g., Inflectra, Remicade, Renflexis): Approve for 3 years if the patient has had a response (e.g., decreased stool frequency or rectal bleeding), as determined by the prescriber. The patient may not have a full response, but there should have been a recent or past response to infliximab.

Remicade is approved in pediatric patients ≥ 6 years of age with ulcerative colitis; although Inflectra and Renflexis do not share this indication, the prescribing information notes that pediatric assessment demonstrated safety and efficacy in this indication.[117] Infliximab has been effective in cases of refractory pouchitis.[34] Clinical guidelines for the management of pouchitis, published in 2009, and ulcerative colitis practice guidelines from the American College of Gastroenterology (ACG) [2010] indicate that first-line therapy for pouchitis is antibiotic therapy (e.g. metronidazole, ciprofloxacin).[35-36] Other treatment options include maintenance probiotics, oral or topical budesonide, anti-inflammatory drugs (e.g. mesalamine), or immunosuppressive drugs (e.g. Infliximab).

Other Uses with Supportive Evidence

7. Behcet's Disease: Approve for 1 year if the patient meets the following criteria (A and B):

A) The patient meets ONE of the following conditions (i or ii):
  i. The patient has tried at least ONE conventional therapy (e.g., systemic corticosteroids [for example, methylprednisolone], immunosuppressants [for example, azathioprine, methotrexate {MTX}, mycophenolate mofetil, cyclosporine, tacrolimus, Leukeran® [chlorambucil], cyclophosphamide, interferon alfa).
  NOTE: An exception to the requirement for a trial of one conventional therapy can be made if the patient has already had a trial of at least one biologic (e.g., Humira [adalimumab SC injection] or Enbrel [etanercept SC injection]). These patients who have already tried a biologic for Behcet's disease are not required to "step back" and try a conventional therapy); OR
  ii. The patient has ophthalmic manifestations of Behcet's disease; AND
B) Infliximab (e.g., Inflectra, Remicade, Renflexis) is prescribed by or in consultation with a rheumatologist, dermatologist, ophthalmologist, gastroenterologist, or neurologist.

Numerous case series have reported that infliximab is effective in producing short-term remission of Behcet's disease, especially uveitis, in patients who were refractory to corticosteroids and conventional immunosuppressive therapy.[37-38] EULAR recommendations for the management of Behcet's disease include either infliximab or cyclosporine in combination with azathioprine and corticosteroids for refractory eye involvement.[39] Recommendations for the use of TNF blockers in ocular inflammatory disorders from the American Academy of Ophthalmology (AAO) [2014] notes that infliximab may be used first-line in patients with ophthalmic manifestations of Behcet's disease and for acute exacerbations of pre-existing Behcet's disease.[40] For gastrointestinal (GI) or parenchymal involvement, TNF antagonists have been used in resistant and complicated cases.

8. Graft-Versus-Host Disease (GVHD): Approve for 1 year if the patient meets the following criteria (A and B):
A) The patient meets ONE of the following conditions (i or ii):
  i. Patient has tried one conventional treatment for graft-versus-host disease (GVHD) [e.g., a high-dose corticosteroid such as methylprednisolone, antithymocyte globulin, cyclosporine, Thalomid® {thalidomide capsules}, tacrolimus, mycophenolate mofetil]; OR
  ii. Patient is concurrently receiving at least one of these medications (e.g., a high-dose corticosteroid such as methylprednisolone, antithymocyte globulin, cyclosporine, Thalomid, tacrolimus, mycophenolate mofetil) in combination with infliximab (e.g., Inflectra, Remicade, Renflexis); AND
B) Infliximab (e.g., Inflectra, Remicade, Renflexis) is prescribed by or in consultation with an oncologist, hematologist, or a physician affiliated with a transplant center.

Studies suggest that TNF-α is a major mediator in acute GVHD.[41-42] In retrospective analyses and case series, infliximab has been effective in treating some patients with steroid-refractory acute or chronic graft-versus-host disease.[41-46] In a prospective study in 19 patients, infliximab was not effective in the *prophylaxis* of acute GVHD, but may have delayed platelet engraftment and was associated with frequent infectious complications.[42] In studies evaluating the role of infliximab for treatment of steroid-refractory acute GVHD, the overall response rates ranged from 15% to 100%, with the highest response rates in patients with GI and skin disease.[41]

9. Hidradenitis Suppurativa: Approve for 1 year if the patient meets the following criteria (A and B):
A) The patient has tried one other therapy (e.g., intralesional or oral corticosteroids [such as triamcinolone, prednisone], systemic antibiotics [for example, clindamycin, dicloxacillin, erythromycin], isotretinoin); AND

B) Infliximab (e.g., Inflectra, Remicade, Renflexis) is prescribed by or in consultation with a dermatologist.

In a Phase II double-blind, placebo-controlled crossover trial, adult patients with moderate to severe hidradenitis suppurativa were randomized to placebo (n = 23) or infliximab 5 mg/kg (n = 15) at Weeks 0, 2, and 6.[47] After Week 8, patients were unblinded, and placebo patients were offered induction with placebo. Maintenance was continued through 22 weeks of treatment. Following Week 8, more patients in the infliximab-treatment group experienced a 50% or greater decrease in the Hidradenitis Suppurativa Severity Index (HSSI) score (approximately 26% and 5% of patients receiving infliximab and placebo, respectively [data presented graphically]; P = 0.092). In post-hoc analysis, significantly more patients treated with infliximab responded with a 25% to < 50% response (60% and 5.6% for infliximab and placebo, respectively; P < 0.001). Improvement was noted through Week 30. In case series, Remicade has been effective in treating hidradenitis suppurativa that was refractory to other therapies.[48-50]

10. Indeterminate Colitis in a Patient ≥ 6 Years of Age (defined as colitis that cannot be classified with certainty as either ulcerative colitis or Crohn's disease): Approve for 1 year if the patient meets ALL of the following criteria (A, B, C, and D):
A) Patient has tried one systemic corticosteroid (e.g., prednisone, methylprednisolone); AND
B) Patient has tried mesalamine; AND
C) Patient has tried either azathioprine or 6-mercaptopurine; AND
D) Infliximab (e.g., Inflectra, Remicade, Renflexis) is prescribed by or in consultation with a gastroenterologist.

Infliximab has been effective in some patients with refractory indeterminate colitis (retrospective reviews).[51-52] When patients who are refractory to standard therapy can be definitively classified as having ulcerative colitis, colectomy is considered an effective long-term surgical treatment. Patient's with Crohn's disease, however, have a high risk of complications after ileal pouch-anal anastomosis and are treated more aggressively with medical interventions since surgical options cannot offer the same likelihood of success as in ulcerative colitis.

11. Juvenile Idiopathic Arthritis (JIA) [or Juvenile Rheumatoid Arthritis {JRA}] (regardless of type of onset) [Note: This includes patients with juvenile spondyloarthropathy/active sacroiliac arthritis]: Approve for the duration noted if the patient meets ONE of the following (A or B):
A) Initial Therapy: Approve for 3 months if the patient meets the following criteria (i and ii):
  i. Patient meets ONE of the following conditions (a or b):
    a) Patient has tried one other agent for this condition (e.g., methotrexate [MTX], sulfasalazine, or leflunomide, a nonsteroidal anti-inflammatory drug [NSAID] {e.g., ibuprofen, naproxen}).
    (NOTE: A previous trial of a biologic [e.g., Humira {adalimumab SC injection], Orencia {abatacept IV infusion, abatacept SC injection}, Enbrel {etanercept SC injection}, Kineret {anakinra SC injection}, Actemra {tocilizumab IV infusion}] also counts as a trial of one agent for JIA); OR
    b) Patient has aggressive disease, as determined by the prescribing physician; AND
  ii. Infliximab (e.g., Inflectra, Remicade, Renflexis) is prescribed by or in consultation with a rheumatologist.
B) Patients Currently Receiving Infliximab (e.g., Inflectra, Remicade, Renflexis): Approve for 3 years if the patient has had a response (e.g., has improvement in limitation of motion; less joint pain or tenderness; decreased duration of morning stiffness or fatigue; improved function or

activities of daily living; reduced dosage of corticosteroids), as determined by the prescriber. The patient may not have a full response, but there should have been a recent or past response to infliximab.

Enbrel, Humira, Orencia SC and IV, and Actemra IV are indicated for moderately to severely active polyarticular JIA in patients aged ≥ 2 years (≥ 6 years for Orencia IV formulation). Limited information is available for use of infliximab in JIA.[1,53-58] The 2011 ACR recommendations for the treatment of JIA propose initial DMARD treatment with MTX in most patients; however, sulfasalazine is recommended for patients with enthesitis-related arthritis and may also be used in certain patients with sacroiliac arthritis.[55] Leflunomide may be an appropriate initial DMARD in those with high disease activity and/or a poor prognosis. Kineret may be used in systemic arthritis and Actemra may be used in systemic and polyarticular juvenile arthritis.[55,59] TNF antagonists such as infliximab may also be used as second- or third-line treatment for systemic JIA.[55]

12. Pyoderma Gangrenosum: Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** The patient meets ONE of the following conditions (i or ii):
  - **i.** The patient has tried one systemic corticosteroid (e.g., prednisone); OR
  - **ii.** The patient has tried one other immunosuppressant (e.g., mycophenolate mofetil, cyclosporine) for at least 2 months or was intolerant to one of these agents; AND
- **B)** Infliximab (e.g., Inflectra, Remicade, Renflexis) is prescribed by or in consultation with a dermatologist.

The mainstay of treatment of pyoderma gangrenosum is immunosuppression.[60] Multiple topical and systemic therapies have been used to treat pyoderma gangrenosum. Oral prednisone is the most common initial immunosuppressant medication.[61-62] Topical therapies (e.g., corticosteroids, immunomodulators) may be applied to the lesion. Other systemic therapies used for treatment of pyoderma gangrenosum include cyclosporine, MTX, azathioprine, cyclophosphamide, mycophenolate mofetil, infliximab, Enbrel, and Humira. Infliximab has been an effective treatment in pyoderma gangrenosum refractory to other therapies.[63-64] In a small multicenter, double-blind study, patients with pyoderma gangrenosum were randomized to an infusion of infliximab 5 mg/kg (n = 13) or placebo (n = 17) at Week 0.[65] Patients were assessed at Week 2 and nonresponders (n = 23) were offered open-label infliximab and assessed at Weeks 4 and 6. At Week 2, significantly more patients on Infliximab had improved (46% of patients on infliximab [n = 6/13] vs. 6% of patients with placebo [n = 1/17]; P = 0.025). In all, 29 patients received infliximab with 69% showing a beneficial clinical response. The remission rate at Week 6 was 21%; there was no response in 31% of patients (n = 9/29). In the professional opinion of specialist physicians reviewing the data, we have adopted the criteria requirements for previous therapy. A systematic review of IBD-associated pyoderma gangrenosum identified 60 cases published in the literature.[66] In total, 85% of patients (n = 29/34) treated with infliximab demonstrated healing, with a single dose or induction only effective in 50% of patients (n = 17/34).

13. Sarcoidosis: Approve for 1 year if the patient meets ALL of the following criteria (A, B, and C):
- **A)** Patient has tried at least one corticosteroid (e.g., prednisone); AND
- **B)** Patient has tried at least one immunosuppressive agent (e.g., methotrexate [MTX], azathioprine, cyclosporine, Leukeran) or Thalomid® (thalidomide capsules) or chloroquine; AND
- **C)** Infliximab (e.g., Inflectra, Remicade, Renflexis) is prescribed by or in consultation with a pulmonologist, ophthalmologist, or dermatologist.

Well-controlled studies are not available for any therapies.[67] Steroids are the standard therapy, but long-term use is limited by adverse events. Immunosuppressants have shown modest efficacy with the best results available for MTX. High levels of TNF in bronchoalveolar lavage of patients with sarcoidosis have been reported with a decrease in TNF levels following treatment. Infliximab has been effective in controlling various manifestations of sarcoidosis in selected patients who were refractory to standard therapy.[60,68-74] In a Phase II, multicenter, double-blind trial, 138 patients with corticosteroid-dependent chronic pulmonary sarcoidosis were randomized to Infliximab 3 or 5 mg/kg or to placebo at Weeks 0, 2, 6, 12, 18, and 24 and were followed through Week 54.[75] The mean change from baseline to Week 24 in percent of predicted forced vital capacity (FVC) was an increase of 2.5% with infliximab (both groups combined) vs. no change with placebo (P = 0.038). There were no significant differences between treatment groups for any of the major secondary endpoints at Week 24.[75-76] The clinical relevance of the FVC improvement is unclear. In a post hoc analysis, patients with more severe disease tended to benefit more from infliximab.[75]

14. **Scleritis or Sterile Corneal Ulceration:** Approve for 1 year if the patient meets BOTH of the following criteria (A and B):
    - **A)** The patient has tried one other therapy for this condition (e.g., oral non-steroidal anti-inflammatory drugs [NSAIDs] such as indomethacin, naproxen, or ibuprofen; oral, topical [ophthalmic] or intravenous corticosteroids [such as prednisone, prednisolone, methylprednisolone]; methotrexate [MTX]; cyclosporine; or other immunosupressants); AND
    - **B)** Infliximab (e.g., Inflectra, Remicade, Renflexis) is prescribed by or in consultation with an ophthalmologist.

    Recommendations for the use of TNF blockers in ocular inflammatory disorders from the AAO (2014) note that infliximab may be used as second-line corticosteroid-sparing therapy for chronic and severe scleritis.[40] In an open-label study (n = 5) with active anterior scleritis who had tried at least one conventional therapy, patients received infliximab 5 mg/kg at Weeks 0, 2, and 6 followed by an infusion every 4 weeks through Week 30. All five patients achieved control of symptoms by Week 14.[77] Four of five patients completed the study, tapered other immunosuppressant medications, and had stable visual acuity. In a separate review of patients (n = 10) with scleritis refractory to standard therapy treated with infliximab 5 mg/kg every 4 to 8 weeks, 100% of patients achieved a favorable response and six patients achieved remission.[78] Other patient reviews have documented small numbers of patients who have had either a partial or complete response to infliximab for treatment of scleritis.[79-82] Cases of corneal ulceration have also been treated successfully with infliximab.[83]

15. **Still's Disease**: Approve for 1 year if the patient meets ALL of the following criteria (A, B, and C):
    - **A)** Patient has tried one corticosteroid (e.g., prednisone); AND
    - **B)** Patient has tried one conventional synthetic DMARD such as methotrexate given for at least 2 months or was intolerant to a conventional synthetic DMARD; AND
    - **C)** Infliximab (e.g., Inflectra, Remicade, Renflexis) is prescribed by or in consultation with a rheumatologist.

    Still's disease presents in adults with features similar to those of systemic onset JIA.[84-85] In case series, infliximab has been effective in patients with Still's disease that was refractory to therapy with corticosteroids, MTX, azathioprine, and cyclophosphamide.[86]

16. **Spondyloarthritis (SpA), Subtypes Other than Ankylosing Spondylitis or Psoriatic Arthritits** (e.g., undifferentiated arthritis, non-radiographic axial SpA, Reactive Arthritis [Reiter's disease])

[NOTE: For AS or PsA, refer to the respective criteria under FDA-approved indications]: Approve for one year if BOTH of the following conditions are met (A and B):

A) The patient meets one of the following conditions (i or ii):
- **i.** The patient has arthritis primarily in the knees, ankles, elbows, wrists, hands, and/or feet AND has tried at least ONE conventional synthetic DMARD (e.g., methotrexate [MTX], leflunomide, sulfasalazine) has been tried; OR
- **ii.** The patient has axial spondyloarthritis; AND

B) Infliximab (e.g., Inflectra, Remicade, Renflexis) is prescribed by or in consultation with a rheumatologist.

SpA describes a group of inter-related rheumatic conditions that are distinguished according to their clinical presentation.[87-88] (Note that AS and PsA are specific subtypes of SpA for which infliximab is indicated and criteria are addressed in the FDA-approved indications of this policy.) SpA involves sites where ligaments and tendons attach to bones (entheses). Symptoms often include inflammation that leads to pain and stiffness. Axial SpA refers to inflammatory disease with a main symptom of back pain and includes AS (where x-ray damage is clearly present) and non-radiographic axial (nr-ax)SpA.[89] In nr-axSpA, x-ray changes are not present, but there are symptoms. Upon magnetic resonance imaging (MRI), most patients with nr-axSpA have visible inflammation in the sacroiliac joints and/or the spine. Guidelines (2015) for AS and nr-axSpA are available from ACR/Spondylitis Association of America (SAA)/SPARTAN.[19] TNF inhibitors are recommended for patients with nr-axSpA who have tried NSAIDs. Treatment recommendations for axial spondyloarthritis are available from ASAS.[90] These guidelines note that patients who present with axial SpA, including patients with nr-axSpA, should have a trial of at least two NSAIDS over a 4-week period at the maximum recommended or tolerated dose. Patients who have predominantly axial manifestations are not recommended for a conventional synthetic DMARD trial prior to beginning therapy with a TNF blocker. In patients with symptomatic peripheral arthritis, a therapeutic trial of a conventional synthetic DMARD is recommended (preferably sulfasalazine).

17. Uveitis (including other posterior uveitides and panuveitis syndromes): Approve for 1 year if the patient meets BOTH of the following criteria (A and B):

A) The patient has tried one of the following therapies: periocular, intraocular, or systemic corticosteroids (for example, triamcinolone, betamethasone, methylprednisolone, prednisone) or immunosuppressives (e.g., methotrexate [MTX], mycophenolate mofetil, cyclosporine, azathioprine, cyclophosphamide).
(NOTE: An exception to the requirement for a trial of one of these therapies can be made if the patient has already had a trial of Enbrel or Humira for uveitis. These patients who have already tried a biologic for uveitis are not required to try a another agent); AND

B) Infliximab (e.g., Inflectra, Remicade, Renflexis) is prescribed by or in consultation with an ophthalmologist.

In patients with uveitis, TNF levels are increased in the serum and aqueous humor.[91] Infliximab has been effective in producing regression of symptoms and improving visual acuity in patients with panuveitis, posterior or anterior uveitis, scleritis, and retinal vasculitis; many of these patients have an underlying extraocular systemic diagnosis such as RA, ankylosing spondylitis, psoriasis, spondyloarthropathy, JIA, Behcet's disease, or Crohn's disease who were refractory to corticosteroids and immunosuppressive agents.[91-92] Recommendations for the use of TNF blockers in ocular inflammatory disorders from the AAO (2014) note that Infliximab may be used in patients with uveitis due to various causes (e.g., spondyloarthropathy-associated or human leukocyte antigen [HLA]-B27-associated uveitis, JIA-associated uveitis, and other posterior uveitides and panuveitis

syndromes).[40] Infliximab should be considered second-line in vision-threatening JIA-associated uveitis when MTX has failed or is not tolerated (strong recommendation) and vision-threatening chronic uveitis from seronegative spondyloarthropathy (strong recommendation). Infliximab may also be considered in other patients who have vision-threatening or corticosteroid-dependent disease who have failed first-line therapies. The recommendations point out that studies evaluating Infliximab in uveitis included patients with birdshot chorioretinitis (BSCR), a bilateral posterior uveitis generally treated with systemic immunomodulation; these patients showed a good response to Infliximab.

18. **Patient has been Established on Infliximab (e.g., Inflectra, Remicade, Renflexis) for ≥ 90 Days:** For conditions that do not have criteria for Patients Currently Receiving Infliximab but are indications or conditions addressed as an approval in the Recommended Authorization Criteria section (FDA-Approved Indications and Other Uses with Supportive Evidence), approve Remicade for 1 year, if the patient is currently taking infliximab for ≥ 90 days. (In the professional opinion of specialist physicians reviewing the data, we have adopted this criterion.)

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Infliximab has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Concurrent Use with a Biologic or with a Targeted Synthetic DMARD:** Infliximab should not be administered in combination with another biologic or with a targeted synthetic DMARD used for an inflammatory condition (see APPENDIX for examples). Combination therapy is generally not recommended due to a higher rate of adverse effects with combinations and lack of additive efficacy.[93, 115] Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., MTX, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with infliximab.

2. **Inflammatory Myopathies (Polymyositis, Dermatomyositis, Inclusion Body Myositis):** Exceptions are not recommended. In an open-label pilot study in 13 patients, four infliximab 5 mg/kg infusions given over 14 weeks were not effective in refractory inflammatory myopathies.[94] Infliximab could worsen muscle inflammation in these patients.

3. **Large Vessel Vasculitis (e.g., Giant Cell Arteritis, Takayasu's Arteritis):** Guidelines from EULAR for the management of large vessel vasculitis (e.g., giant cell arteritis, Takayasu's arteritis) do not mention the use of TNF blockers.[95] Additionally, a meta-analysis of RCTs did not find evidence supporting remission or reduction of corticosteroid dose with the use of TNF blockers in large vessel vasculitis.[96] In a controlled trial, 44 patients with newly diagnosed giant cell arteritis that was in glucocorticoid-induced remission were randomized to Infliximab 5 mg/kg plus glucocorticoid (n = 28) or placebo plus glucocorticoid (n = 16).[97] Infliximab did not increase the percentage of patients without relapse at Week 22 nor did it increase the percentage of patients whose glucocorticoid dose was decreased to 10 mg/day without relapse. Use of TNF blockers such as infliximab for Takayasu's arteritis is limited to case series where TNF blockers are often used third line, after treatment with corticosteroids and other immunosuppressants (e.g., azathioprine, MTX, MMF, cyclophosphamide).[98-102] Infliximab has been effective in a very limited number of patients with vasculitis (e.g., RA, cryoglobulinemia, polyangiitis, polymyalgia rheumatica, Takayasu's arteritis) who were refractory to standard therapy.[98-99,103-107] However, in a randomized study in 51

patients with newly diagnosed polymyalgia rheumatica, adding Infliximab 3 mg/kg to prednisone was of no benefit and may have been harmful.[108-109]

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date
Annual revision	Remove "in an adult" as a condition for approval in RA. Throughout the policy, when a trial of a medication from a drug class is required prior to approval of Remicade, add examples of specific medications in that drug class that may have been tried. Add Otezla as an example of a targeted synthetic DMARD that should not be used in combination with Remicade.	06/17/2015
Selected revision	Update previous therapy required in the RA criteria. Criteria now require a trial of a conventional synthetic DMARD. There is an exception for patients who have already tried a biologic; these patients are not required to "step back" and try a conventional synthetic DMARD. Remove other exceptions for patients who are not required to try a conventional synthetic DMARD prior to this biologic. For RA and JIA, remove requirement that Remicade be taken in combination with a conventional synthetic DMARD such as MTX. Add criteria for SpA and delete criteria for Undifferentiated Spondyloarthritis (a condition now covered under SpA).	01/06/2016
Selected revision	For psoriasis, the criterion that allows an exception for patients with a contraindication to one traditional oral therapy is being adjusted to specify a contraindication to MTX. In addition, the psoriasis criteria concerning previous therapy are being reworded for clarification.	04/06/2016
Annual revision	Remove the following Conditions Not Recommended for Approval which do not come up (remain denials but are not addressed in the policy); Chronic Idiopathic Orbital Inflammation (Orbital Myositis), Cogan's Syndrome, Diffuse Cutaneous Systemic Sclerosis (Scleroderma, SSc), Macular Edema in Patients with Type 2 Diabetes, MDS, Primary Sclerosing Cholangitis, Primary Sjögren's Syndrome, Renal Cell Carcinoma, SAPHO syndrome,—Wegener's Granulomatosis. In Conditions Not Recommended for Approval, combine related indications (i.e., Giant Cell Arteritis [a form of Systemic Vasculitis]; Takayasu's Arteritis; and Vasculitis, Systemic) under the diagnosis of Large Vessel Vasculitis (e.g., Giant Cell Arteritis, Takayasu's Arteritis).	06/22/2016
11/02/2016	Add Inflectra to the policy. Approve Inflectra with the same criteria as are in place for Remicade. Rename policy (From Inflammatory Conditions – Remicade PA Policy to Inflammatory Conditions – Infliximab Products (Inflectra/Remicade).	11/02/2016
Annual revision	Clarify criteria for Crohn's disease, ulcerative colitis, Behcet's disease, JIA, and uveitis. For these conditions, the criterion that directs patients to previous therapy prior to approval of infliximab was reworded to clarify its intent such that patients are now directed to conventional agents with a note that prior use of a biologic would count towards this requirement. Previously, criteria were worded more generally and both conventional and biologic therapies were listed.	06/28/2017
Selected revision	Add Renflexis to the policy with the same criteria as Inflectra and Remicade.	07/26/2017
Selected revision	For initial therapy of plaque psoriasis, add criteria to require that the patient be to be at least 18 years of age.	10/18/2017

TAC – Therapeutic Assessment Committee; DEU – Drug Evaluation Unit; TAC – Therapeutic Assessment Committee; * For a further summary of criteria changes, refer to respective TAC minutes available at: http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx; CD – Crohn's disease; COPD – Chronic obstructive pulmonary disease; DMARD – Disease-modifying antirheumatic drug; JIA – Juvenile idiopathic arthritis; RA – Rheumatoid arthritis; SpA – Spondyloarthritis; MTX – Methotrexate; MDS – Myelodysplastic syndrome; SAPHO – Synovitis, Acne, Pustulosis, Hyperostosis, Osteotis.

APPENDIX

Brand (generic name)	Mechanism of Action
Cimzia® (certolizumab pegol for SC injection)	Inhibition of TNF
Enbrel® (etanercept for SC injection)	Inhibition of TNF
Erelzi™ (etanercept-szzs for SC injection)	Inhibition of TNF
Humira® (adalimumab for SC injection)	Inhibition of TNF
Amjevita® (adalimumab-atto for SC injection)	Inhibition of TNF
Simponi® (golimumab for SC injection)	Inhibition of TNF
Simponi® Aria™ (golimumab for IV infusion)	Inhibition of TNF
Remicade® (infliximab for IV infusion)	Inhibition of TNF
Inflectra™ (infliximab-dyyb for IV infusion)	Inhibition of TNF
Renflexis® (infliximab-abda for IV infusion)	Inhibition of TNF
Actemra® (tocilizumab for IV infusion)	Inhibition of IL-6
Actemra® (tocilizumab for SC injection)	Inhibition of IL-6
Kevzara® (sarilumab for SC injection)	Inhibition of IL-6
Orencia® (abatacept for IV infusion)	T-cell costimulation modulator
Orencia® (abatacept for SC injection)	T-cell costimulation modulator
Rituxan® (rituximab for IV infusion)	CD20-directed cytolytic antibody
Kineret® (anakinra for subcutaneous SC injection)	Inhibition of IL-1
Stelara® (ustekinumab for SC injection)	Inhibition of IL-12/23
Stelara® (ustekinumab for IV infusion)	Inhibition of IL-12/23
Siliq™ (brodalumab SC injection)	Inhibition of IL-17
Cosentyx™ (secukinumab for SC injection)	Inhibition of IL-17A
Taltz® (ixekizumab for SC injection)	Inhibition of IL-17A
Tremfya™ (guselkumab for SC injection)	Inhibition of IL-23
Otezla® (apremilast tablets)	Inhibition of PDE4
Xeljanz®, Xeljanz XR (tofacitinib tablets, tofacitinib extended-release tablets)	Inhibition of the JAK pathways

SC – Subcutaneous; TNF – Tumor necrosis factor; IV – Intravenous, IL – Interleukin; PDE4 – Phosphodiesterase 4; JAK – Janus kinase.