PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Infliximab Products Prior Authorization Policy
- Avsola™ (infliximab-axxq intravenous infusion – Amgen)
- Inflectra™ (infliximab-dyyb intravenous infusion – Hospira/Pfizer)
- Remicade® (infliximab intravenous infusion – Janssen Biotech, Inc./Johnson & Johnson)
- Renflexis® (infliximab-abda intravenous infusion – Samsung Bioepis/Merck)

REVIEW DATE: 09/23/2020

OVERVIEW

Infliximab products are tumor necrosis factor inhibitors (TNFis) approved for the following indications:[1-3]
- **Ankylosing spondylitis**, for reducing signs and symptoms of active disease.
- **Crohn's disease**, for the following uses:
  - Reducing the signs and symptoms and inducing and maintaining clinical remission in patients ≥ 6 years of age with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy; AND
  - Reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adults with fistulizing Crohn's disease.
- **Plaque psoriasis**, for treatment of adults with chronic severe (i.e., extensive and/or disabling) disease who are candidates for systemic therapy and when other systemic therapies are less appropriate.
- **Psoriatic arthritis**, for reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage and improving physical function.
- **Rheumatoid arthritis**, in combination with methotrexate for reducing signs and symptoms, inhibiting the progression of structural damage and improving physical function in patients with moderately to severely active disease.
- **Ulcerative colitis**, for the following uses:
  - Reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adults with moderately to severely active disease who have had an inadequate response to conventional therapy; AND
  - Reducing signs and symptoms and inducing and maintaining clinical remission in patients ≥ 6 years of age with moderately to severely active disease who have had an inadequate response to conventional therapy.

Avsola, 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.[2-3] However, minor differences in clinically inactive components are allowed. At this time, only biosimilarity has been demonstrated (not interchangeability).

Guidelines

TNFis feature prominently in guidelines for treatment of many inflammatory conditions.
- **Spondyloarthritis:** Guidelines for ankylosing spondylitis and non-radiographic axial spondyloarthritis are published by the American College of Rheumatology (ACR)/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network (2019).[4] Following primary nonresponse to a TNFi, an interleukin (IL)-17 blocker is recommended; however, if the patient is a secondary nonresponder, a second TNFi is recommended over switching out of the

class. In patients with a contraindication to a TNFi, use of an IL-17 blocker is recommended over traditional oral agents such as methotrexate or sulfasalazine.

- **Crohn's Disease:** The American College of Gastroenterology (ACG) has guidelines for Crohn's disease (2018).[5] TNFis are listed as an option for disease that is resistant to corticosteroids, severely active disease, perianal fistulizing disease, and maintenance of remission. In post-operative Crohn's disease, a TNFi should be started within 4 weeks of surgery to prevent recurrence.
- **Plaque Psoriasis:** Guidelines from the American Academy of Dermatologists (AAD) and National Psoriasis Foundation (NPF) [2019] recommend infliximab as a monotherapy treatment option for adults with moderate to severe disease.[6]
- **Psoriatic Arthritis:** Guidelines from ACR (2019) recommend TNFis over other biologics for use in treatment-naïve patients with psoriatic arthritis, and in those who were previously treated with an oral therapy.[7]
- **Rheumatoid Arthritis:** Guidelines from the American College of Rheumatology (ACR) [2015] have TNF inhibitors and non-TNF biologics, administered with or without methotrexate, equally positioned as a recommended therapy following a trial of a conventional synthetic disease-modifying antirheumatic drug (DMARD) [e.g., methotrexate, leflunomide, hydroxychloroquine, sulfasalazine].[8]
- **Ulcerative Colitis:** Updated ACG guidelines for ulcerative colitis (2019) note that the following agents can be used for induction of remission in moderately to severely active disease: Uceris tablets; Oral or intravenous systemic corticosteroids Entyvio, Xeljanz, or TNFis.[9] In addition to the approved indication, clinical guidelines for the management of pouchitis, published in 2009 indicate that first-line therapy for pouchitis is antibiotic therapy (e.g. metronidazole, ciprofloxacin).[11] Other treatment options include maintenance probiotics, oral or topical budesonide, anti-inflammatory drugs (e.g., mesalamine), or immunosuppressive drugs (e.g., infliximab). Guidelines from the American Gastroenterological Association (2020) recommend infliximab for moderate to severe ulcerative colitis.[11]

Other Uses with Supportive Evidence

There are guidelines and/or published data supporting the use of infliximab products in the following conditions:

- **Behcet's Disease:** The European League Against Rheumatism (EULAR) recommendations (2018) include TNFis for initial or recurrent sight-threatening uveitis.[12] For patients refractory to first-line treatments (e.g., corticosteroids), TNFis are among the treatment options for mucocutaneous manifestations, venous thrombosis, severe or refractory gastrointestinal disease, and recurrent/chronic joint involvement. Recommendations for the use of TNFis in ocular inflammatory disorders from the American Academy of Ophthalmology (AAO) [2014] notes that TNFis may be used first-line in patients with ophthalmic manifestations of Behcet's disease and for acute exacerbations of pre-existing Behcet's disease.[13]
- **Graft-Versus-Host Disease:** Guidelines from the National Comprehensive Cancer network (NCCN) [version 2.2020 – March 23, 2020] list infliximab among the agents used for steroid-refractory disease.[19]
- **Hidradenitis Suppurativa:** 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.[25] 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, infliximab has been effective in treating hidradenitis suppurativa that was refractory to other therapies.[26-28]

- **Indeterminate Colitis:** Infliximab has been effective in some patients with refractory indeterminate colitis (retrospective reviews).[29,30] 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.
- **Ocular Inflammatory Disorders:** Recommendations for the use of TNFis 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.[13] Infliximab may be used in patients with uveitis due to various causes (e.g., spondyloarthropathy-associated or human leukocyte antigen [HLA]-B27-associated uveitis, juvenile idiopathic arthritis-associated uveitis, and other posterior uveitides and panuveitis syndromes).[13] Infliximab should be considered second-line in vision-threatening JIA-associated uveitis when methotrexate 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.
- **Immunotherapy-Related Toxicities Associated with Checkpoint Inhibitors:** NCCN has guidelines (version 1.2020 – December 16, 2020) for Management of Immunotherapy-Related Toxicities.[14] Infliximab is recommended to manage inflammatory arthritis, vision changes, and diarrhea/colitis. Some severe toxicities (e.g., pneumonitis, cardiac toxicity, renal failure) may also be treated with infliximab but are more likely to be administered in the hospital setting.
- **Juvenile Idiopathic Arthritis (JIA):** The ACR/Arthritis Foundation Guideline for the treatment of JIA (2019) provides updated recommendations for juvenile non-systemic polyarthritis, sacroiliitis, and enthesitis.[15] Infliximab is among the TNFis recommended as subsequent therapy following treatment with a conventional synthetic DMARD such as methotrexate. TNF antagonists such as infliximab may also be used as second- or third-line treatment for systemic JIA.[16]
- **Pyoderma Gangrenosum:** Although guidelines are not current, multiple topical and systemic therapies have been used for pyoderma gangrenosum. Oral prednisone is the most common initial immunosuppressant medication.[17] Other systemic therapies include cyclosporine, methotrexate, azathioprine, cyclophosphamide, mycophenolate mofetil, and TNFis (i.e., infliximab, etanercept, and adalimumab products). In case reports, TNFis have been effective.
- **Still's Disease:** Still's disease presents in adults with features similar to those of systemic onset JIA.[31-32] In case series, infliximab has been effective in patients with Still's disease that was refractory to therapy with corticosteroids, methotrexate, azathioprine, and cyclophosphamide.[33]
- **Sarcoidosis:** Recommendations for best practice in the management of pulmonary and systemic sarcoidosis recommend glucocorticoids as first-line therapy.[18] Patients who cannot be weaned to a prednisone-equivalent dose of < 10 mg/day are appropriate candidates for steroid-sparing treatment with cytotoxic agents (e.g., methotrexate, azathioprine, leflunomide). If these agents fail or cause toxicity, adalimumab, infliximab, cyclophosphamide, or mycophenolate mofetil are proposed.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of infliximab products. 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 products is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Ankylosing Spondylitis.** 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)** Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient had a response as determined by the prescriber.
     Note: Examples of a response to therapy include decreased pain or stiffness, improved function or activities of daily living. Patient may not have a full response, but there should have been a recent or past response to an infliximab product.

2. **Crohn's Disease.** 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.** Patient is ≥ 6 years of age; AND
     - **ii.** Patient meets ONE of the following conditions (a, b, c, or d):
       - **a)** Patient has tried or is currently taking corticosteroids, or corticosteroids are contraindicated in this patient; OR
         Note: Examples of corticosteroids are prednisone and methylprednisolone.
       - **b)** Patient has tried one other conventional systemic therapy for Crohn's disease; OR
         Note: Examples of conventional systemic therapies for Crohn's disease include azathioprine, 6-mercaptopurine, or methotrexate. A previous trial of a biologic also counts as a trial of one other agent for Crohn's disease. Refer to Appendix for examples of biologics used for Crohn's disease.
       - **c)** Patient has enterocutaneous (perianal or abdominal) or rectovaginal fistulas; OR
       - **d)** Patient had ileocolonic resection (to reduce the chance of Crohn's disease recurrence); AND
     - **iii.** The medication is prescribed by or in consultation with a gastroenterologist.
   - **B)** Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient had a response, as determined by the prescriber.
     Note: Patient may not have a full response, but there should have been a recent or past response to an infliximab product.

3. **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.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient meets ONE of the following conditions (a or b):
       - **a)** Patient has tried at least one traditional systemic agent for psoriasis for at least 3 months, unless intolerant; OR

Note: Examples include methotrexate, cyclosporine, acitretin (Soriatane®, generics), or psoralen plus ultraviolet A light (PUVA). An exception to the requirement for a trial of one traditional systemic agent for psoriasis can be made if the patient already had a 3-month trial or previous intolerance to at least one biologic. Refer to Appendix for examples of biologics used for psoriasis. These patients who have already tried a biologic for psoriasis are not required to "step back" and try a traditional systemic agent for psoriasis.

b) Patient has a contraindication to methotrexate, as determined by the prescriber; AND

iii. The medication is prescribed by or in consultation with a dermatologist.

B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient had a response, as determined by the prescriber.
Note: Patient may not have a full response, but there should have been a recent or past response to an infliximab product.

4. Psoriatic 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 prescribed by or in consultation with a rheumatologist or a dermatologist.

B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient had a response as determined by the prescriber.
Note: Examples of a response include 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). Patient may not have a full response, but there should have been a recent or past response to an infliximab product.

5. Rheumatoid 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 BOTH of the following criteria (i and ii):

i. Patient has tried ONE conventional synthetic disease-modifying antirheumatic drug (DMARD) for at least 3 months; AND
Note: Examples include methotrexate (oral or injectable), leflunomide, hydroxychloroquine, and sulfasalazine. An exception to the requirement for a trial of one conventional synthetic DMARD can be made if the patient already had a 3-month trial of at least one biologic. Refer to Appendix for examples of biologics used for rheumatoid arthritis. These patients who have already tried a biologic are not required to "step back" and try a conventional synthetic DMARD.

ii. The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient had a response as determined by the prescriber.
Note: Examples of a response include 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. Patient may not have a full response, but there should have been a recent or past response to an infliximab product.

6. Ulcerative Colitis. 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. Patient is ≥ 6 years of age; AND

ii. Patient meets ONE of the following conditions (a or b):

a) Patient had a trial of one systemic agent or was intolerant to one of these agents for ulcerative colitis; OR

Note: Examples include 6-mercaptopurine, azathioprine, cyclosporine, tacrolimus, or a corticosteroid such as prednisone, methylprednisolone. A previous trial of a biologic also counts as a trial of one systemic agent for ulcerative colitis. Refer to Appendix for examples of biologics used for ulcerative colitis.

b) Patient meets BOTH of the following [(1) and (2)]:
(1) Patient has pouchitis; AND
(2) Patient has tried therapy with an antibiotic, probiotic, corticosteroid enema, or Rowasa® (mesalamine) enema; AND
Note: Examples of antibiotics include metronidazole and ciprofloxacin. Examples of corticosteroid enemas include hydrocortisone enema (Cortenema, generics).

iii. The medication is prescribed by or in consultation with a gastroenterologist.

B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient had a response as determined by the prescriber.
Note: Examples of a response include decreased stool frequency or rectal bleeding. The patient may not have a full response, but there should have been a recent or past response to an infliximab product.

Other Uses with Supportive Evidence

7. Behcet's Disease. Approve for the duration noted if the patient meets the following criteria (A or B):
A) Initial Therapy. Approve for 3 months if the patient meets BOTH of the following conditions (i and ii):
i. Patient meets ONE of the following (a or b):
a) Patient has tried at least ONE conventional therapy; OR
Note: Examples include systemic corticosteroids (e.g., methylprednisolone), immunosuppressants (azathioprine, methotrexate, mycophenolate mofetil, cyclosporine, tacrolimus, Leukeran® [chlorambucil], cyclophosphamide, interferon alfa). 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 tumor necrosis factor inhibitor (e.g., an adalimumab product, an etanercept product). These patients who have already tried a biologic for Behcet's disease are not required to "step back" and try a conventional therapy.
b) Patient has ophthalmic manifestations of Behcet's disease; AND
ii. The medication is prescribed by or in consultation with a rheumatologist, dermatologist, ophthalmologist, gastroenterologist, or neurologist.
B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient had a response, as determined by the prescriber.
Note: Patient may not have a full response by Month 2 or 3, but there should be some response.

8. Graft-Versus-Host Disease. Approve for the duration noted if the patient meets the following criteria (A or B):
A) Initial Therapy. Approve for 1 month if the patient meets BOTH of the following (i and ii):
i. Patient has tried at least one conventional systemic treatment for graft-versus-host disease; AND
Note: Examples of conventional treatments include corticosteroids (e.g., methylprednisolone), antithymocyte globulin, cyclosporine, tacrolimus, and mycophenolate mofetil.
ii. The medication is prescribed by or in consultation with an oncologist, hematologist, or a physician affiliated with a transplant center; OR
B) Patient is Currently Receiving an Infliximab Product. Approve for 3 months if the patient had a response, as determined by the prescriber.

9. Hidradenitis Suppurativa. Approve for the duration noted if the patient meets the following criteria (A or B):
- **A)** Initial Therapy. Approve for 3 months if the patient meets BOTH of the following (i and ii):
  - **i.** Patient has tried one other therapy; AND
    Note: Examples include intralesional or oral corticosteroids (e.g., triamcinolone, prednisone), systemic antibiotics (e.g., clindamycin, dicloxacillin, erythromycin), and isotretinoin.
  - **ii.** The medication is prescribed by or in consultation with a dermatologist.
- **B)** Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient had a response, as determined by the prescriber.

10. Immunotherapy-Related Toxicities Associated with Checkpoint Inhibitor Therapy. 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 ALL of the following (i, ii, iii, and iv):
  - **i.** Patient developed an immunotherapy-related toxicity involving the gastrointestinal system, inflammatory arthritis, or ocular toxicity; AND
    Note: An example of a gastrointestinal system toxicity is colitis. Examples of ocular toxicities include uveitis/iritis, episcleritis, and blepharitis.
  - **ii.** Patient developed this immune-related toxicity while receiving a checkpoint inhibitor; AND
    Note: Examples of checkpoint inhibitors include Keytruda (pembrolizumab intravenous [IV] infusion), Opdivo (nivolumab IV infusion), Yervoy (ipilimumab IV infusion), Tecentriq (atezolizumab IV infusion), Bavencio (avelumab IV infusion), or Imfinzi (durvalumab IV infusion).
  - **iii.** Patient has tried one systemic corticosteroid; AND
    Note: Examples include methylprednisone and prednisone.
  - **iv.** The medication is prescribed by or in consultation with an oncologist, gastroenterologist, rheumatologist, or ophthalmologist; OR
- **B)** Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient has responded and needs continued treatment, as determined by the prescriber.

11. Indeterminate Colitis (defined as colitis that cannot be classified with certainty as either ulcerative colitis or Crohn's disease). Approve for the duration noted if the patient meets ONE of the following (A or B):
- **A)** Initial Therapy. Approve for 4 months if the patient meets ALL of the following (i, ii, iii, iv, and v):
  - **i.** Patient is ≥ 6 years of age; AND
  - **ii.** Patient has tried one systemic corticosteroid; AND
    Note: Examples include prednisone and methylprednisolone.
  - **iii.** Patient has tried mesalamine; AND
  - **iv.** Patient has tried either azathioprine or 6-mercaptopurine; AND
  - **v.** The medication is prescribed by or in consultation with a gastroenterologist.
- **B)** Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient had a response, as determined by the prescriber.

12. Juvenile Idiopathic Arthritis (JIA) [or Juvenile Rheumatoid Arthritis] (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 medication for this condition; OR

Note: Examples of other medications for JIA include methotrexate, sulfasalazine, or leflunomide, a nonsteroidal anti-inflammatory drug (NSAID) [e.g., ibuprofen, naproxen]. A previous trial of a biologic also counts as a trial of one medication. Refer to Appendix for examples of biologics used for JIA.

b) Patient has aggressive disease, as determined by the prescriber; AND

ii. The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient had a response as determined by the prescriber.
Note: Examples of a response include 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. The patient may not have a full response, but there should have been a recent or past response to an infliximab product.

13. Pyoderma Gangrenosum. Approve for the duration noted if the patient meets the following criteria (A or B):

A) Initial Therapy. Approve for 4 months if the patient meets BOTH of the following conditions (i and ii):

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

A) Patient has tried one systemic corticosteroid; OR
Note: An example is prednisone.

B) Patient has tried one other immunosuppressant for at least 2 months or was intolerant to one of these medications; AND
Note: Examples include mycophenolate mofetil and cyclosporine.

ii. The medication is prescribed by or in consultation with a dermatologist; OR

B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient had a response, as determined by the prescriber.
Note: Patient may not have a full response by Month 4 or 5 (after 4 doses), but there should be some response.

14. Sarcoidosis. Approve for the duration noted if the patient meets ONE of the following criteria (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets ALL of the following conditions (i, ii, and iii):

i. Patient has tried at least one corticosteroid; AND
Note: An example is prednisone.

ii. Patient has tried at least one immunosuppressive medication; AND
Note: Examples include methotrexate, azathioprine, cyclosporine, Leukeran, Thalomid® (thalidomide capsules), or chloroquine.

iii. The medication is prescribed by or in consultation with a pulmonologist, ophthalmologist, or dermatologist; OR

B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient had a response, as determined by the prescriber.
Note: The patient may not have a full response by Month 3, but there should be some response.

15. Scleritis or Sterile Corneal Ulceration. Approve for the duration noted if the patient meets ONE of the following criteria (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets BOTH of the following conditions (i and ii):

i. Patient has tried one other therapy for this condition; AND

Note: Examples include oral non-steroidal anti-inflammatory drugs (NSAIDs) such as indomethacin; oral, topical (ophthalmic) or intravenous corticosteroids (such as prednisone, prednisolone, methylprednisolone); methotrexate; cyclosporine; or other immunosuppressants.

ii. The medication is prescribed by or in consultation with an ophthalmologist; OR

B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient had a response as determined by the prescriber.
Note: Examples of a response to therapy include decreased inflammation, reduced use of steroids or immunomodulators, decreased eye pain, redness, and/or photophobia. The patient may not have a full response by Month 2 or 3, but there should be some response.

16. Still's Disease. Approve for the duration noted if the patient meets ONE of the following criteria (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets ALL of the following conditions (i, ii, and iii):

i. Patient has tried one corticosteroid; AND
Note: An example is prednisone.

ii. Patient has tried one conventional synthetic disease-modifying antirheumatic drug (DMARD) given for at least 2 months or was intolerant; AND
Note: An example is methotrexate.

iii. The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient had a response, as determined by the prescriber.
Note: Patient may not have a full response by Month 2 or 3, but there should be some response.

17. Spondyloarthritis, Other Subtypes (Note: Examples of other subtypes include undifferentiated arthritis, non-radiographic axial spondylitis, Reactive Arthritis [Reiter's disease]. For ankylosing spondylitis or psoriatic arthritis, refer to the respective criteria under FDA-approved indications). Approve for the duration noted if ONE of the following conditions are met (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets BOTH of the following conditions (i and ii):

i. Patient meets ONE of the following (a or b):

a) Patient has arthritis primarily in the knees, ankles, elbows, wrists, hands, and/or feet AND has tried at least ONE conventional synthetic disease-modifying antirheumatic drug (DMARD); OR
Note: Examples include methotrexate, leflunomide, and sulfasalazine.

b) Patient has axial spondyloarthritis with objective signs of inflammation, defined as at least one of the following [(1) or (2)]:

(1) C-reactive protein elevated beyond the upper limit of normal for the reporting laboratory; OR

(2) Sacroiliitis reported on magnetic resonance imaging; AND

ii. The medication is prescribed by or in consultation with a rheumatologist; OR

B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient had a response as determined by the prescriber.
Note: Examples of a response include decreased pain or stiffness, improved function or activities of daily living. The patient may not have a full response, but there should have been a recent or past response to an infliximab product.

18. Uveitis (including other posterior uveitides and panuveitis syndromes). Approve for the duration noted if the patient meets ONE of the following criteria (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets BOTH of the following conditions (i and ii):
- **i.** Patient has tried one of the following therapies: periocular, intraocular, or systemic corticosteroids, or immunosuppressives; AND
  Note: Examples of corticosteroids include prednisolone, triamcinolone, betamethasone, methylprednisolone, prednisone. Examples of immunosuppressives include methotrexate, mycophenolate mofetil, and cyclosporine. 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 an etanercept product or an adalimumab product for uveitis. These patients who have already tried a biologic for uveitis are not required to try another medication.
- **ii.** The medication is prescribed by or in consultation with an ophthalmologist.

B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient had a response as determined by the prescriber.
Note: Examples of a response include decreased inflammation, reduced use of steroids or immunomodulators, and improvement in visual acuity. The patient may not have a full response by Month 2 or 3, but there should be some response.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of infliximab products is not recommended in the following situations:

1. **Concurrent Use with a Biologic or with a Targeted Synthetic Disease-Modifying Antirheumatic Drug (DMARD).** Data are lacking evaluating concomitant use of an infliximab product in combination with another biologic or with a targeted synthetic DMARD used for an inflammatory condition (see APPENDIX for examples). Combination therapy with biologics and/or biologics + targeted synthetic DMARDs has a potential for a higher rate of AEs and lack controlled trial data in support of additive efficacy. Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., MTX, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with an infliximab product.

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.[36] 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.[37] 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.[38] 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).[39] 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, cyclophosphamide).[40-44] 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.[40-41,45-49] 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.[50-51]

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

REFERENCES

1. Remicade® injection [prescribing information]. Horsham, PA: Janssen Biotech; June 2018.
2. Inflectra™ injection for IV use [prescribing information]. Lake Forest, IL: Hospira/Pfizer; April 2016.
3. Renflexis injection for IV use [prescribing information]. Whitehouse Station, NJ: Samsung Bioepis/Merck; April 2017.
4. Ward MM, Deodhar A, Gensler LS, et al. 2019 update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network recommendations for the treatment of ankylosing spondylitis and nonradiographic axial spondyloarthritis. *Arthritis Rheumatol*. 2019;(10):1599-1613.
5. Lichtenstein GR, Loftus EV, Isaacs KL, et al. ACG Clinical Guideline: Management of Crohn's Disease in Adults. *Am J Gastroenterol*. 2018;113(4):481-517.
6. Menter A, Strober BE, Kaplan DH, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. *J Am Acad Dermatol*. 2019;80(4):1029-1072.
7. Singh JA, Guyatt G, Ogdie A, et al. 2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the treatment of psoriatic arthritis. *Arthritis Care Res (Hoboken)*. 2019;71(1):2-29.
8. Singh JA, Saag KG, Bridges SL Jr, et al. 2015 American College of Rheumatology Guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatol*. 2016;68(1):1-26.
9. Rubin DT, Ananthakrishnan AN, Siegel CA, et al. ACG clinical guideline: ulcerative colitis in adults. *Am J Gastroenterol*. 2019;114(3):384-413.
10. Pardi DS, D'Haens G, Shen B, et al. Clinical guidelines for the management of pouchitis. *Inflamm Bowel Dis*. 2009;15(9):1424-1431.
11. Feuerstein JD, Isaac s KL, Schneider Y, et al. AGA clinical practice guidelines on the management of moderate to severe ulcerative colitis. *Gastroenterology*. 2020;158:1450-1461.
12. Hatemi G, Christensen R, Bang D, et al. 2018 update of the EULAR recommendations for the management of Behçet's syndrome. *Ann Rheum Dis*. 2018;77(6):808-818.
13. Levy-Clarke 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;121(3):785-796.
14. The NCCN/ASCO Management of Immunotherapy-Related Toxicities (Immune Checkpoint Inhibitor-Related Toxicities) Clinical Practice Guidelines in Oncology (Version 1.2020 – December 16, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed September 18, 2020.
15. Ringold S, Angeles-Han ST, Beukelman T, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the treatment of juvenile idiopathic arthritis: therapeutic approaches for non-systemic polyarthritis, sacroiliitis, and enthesitis. *Arthritis Rheumatol*. 2019;71(6):846-863.
16. Ringold S, Weiss PF, Beukelman T, 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;65(10):2499-2512.
17. Dabade TS, Davis MD. Diagnosis and treatment of the neutrophilic dermatoses (pyoderma gangrenosum, Sweet's syndrome). *Dermatol Ther*. 2011;24(2):273-284.
18. Amin EN, Closser DR, Crouser ED. Current best practice in the management of pulmonary and systemic sarcoidosis. *Ther Adv Respir Dis*. 2014;8(4):111-132.
19. The NCCN Hematopoietic Cell Transplantation (HCT): pre-transplant recipient evaluation and management of graft versus host disease Clinical Practice Guidelines in Oncology (Version 2.2020 – March 23, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on September 18, 2020.
20. Grant A, Gonzalez T, Montgomery MO, et al. Infliximab therapy for patients with moderate to severe hidradenitis suppurativa: a randomized, double-blind, placebo-controlled crossover trial. *J Am Acad Dermatol*. 2010;62(2):205-217.
21. Sullivan TP, Welsh E, Kerdel FA, et al. Infliximab for hidradenitis suppurativa. *Br J Dermatol*. 2003;149:1046-1049.
22. 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;56:624-628.
23. Haslund P, Lee RA, Jemec GB. Treatment of hidradenitis suppurativa with tumour necrosis factor-alpha inhibitors. *Acta Derm Venereol*. 2009;89(6):595-600.
24. Papadakis KA, Treyzon L, Abreu MT, et al. Infliximab in the treatment of medically refractory indeterminate colitis. *Aliment Pharmacol Ther*. 2003;18:741-747.
25. Gornet JM, Couve S, Hassani Z, et al. Infliximab for refractory ulcerative colitis or indeterminate colitis: an open-label multicentre study. *Aliment Pharmacol Ther*. 2003;18:175-181.
26. Riera E, Olivé A, Narváez J, et al. Adult onset Still's disease: review of 41 cases. *Clin Exp Rheumatol*. 2011;29(2):331-336.
27. Pouchot J, Arlet JB. Biological treatment in adult-onset Still's disease. *Best Pract Res Clin Rheumatol*. 2012;26(4):477-487.

28. Kontzias A, Efthimiou P. Adult-onset Still's disease: pathogenesis, clinical manifestations and therapeutic advances. *Drugs.* 2008;68:319-337.
29. Furst DE, Keystone EC, So AK, et al. Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2012. *Ann Rheum Dis*. 2013;72 Suppl 2:ii2-34.
30. Xeljanz® tablets [prescribing information]. New York, NY: Pfizer Inc; February 2016.
31. Dastmalchi, M, Grundtman, C, Alexanderson, H, et al. A high incidence of disease flares in an open pilot study of infliximab in patients with refractory inflammatory myopathies. *Ann Rheum Dis.* 2008;67:1670-1677.
32. Mukhtyar C, Guillevin L, Cid MC, et al. EULAR recommendations for the management of large vessel vasculitis. *Ann Rheum Dis*. 2009;68(3):318-323.
33. Osman M, Pagnoux C, Dryden DM, et al. The role of biological agents in the management of large vessel vasculitis (LVV): a systematic review and meta-analysis. *PLoS One*. 2014 Dec 17;9(12):e115026.
34. Christophi GP, Ciorba MA. Lower Dose Infliximab for Ulcerative Colitis: How Low Can We Go and How Much Can be Saved? *J Clin Gastroenterol*. 2015;49(7):539-540.
35. Tayer-Shifman OE, Ilan O, Tovi H, Tal Y. Cogan's Syndrome – Clinical Guidelines and Novel Therapeutic Approaches. *Clin Rev Allergy Immunol*. 2014;47(1):65-72.
36. Hoffman GS, Merkel PA, Brasington RD, et al. Anti-tumor necrosis factor therapy in patients with difficult to treat Takayasu arteritis. *Arthritis Rheum.* 2004;50:2296-2304.
37. Mekinian A, Néel A, Sibilia J, et al. Efficacy and tolerance of infliximab in refractory Takayasu arteritis: French multicentre study. *Rheumatology (Oxford)*. 2012;51(5):882-886.
38. Buonuomo PS, Bracaglia C, Campana A, et al. Infliximab therapy in pediatric Takayasu's arteritis: report of two cases. *Rheumatol Int*. 2011;31(1):93-95.
39. Molloy ES, Langford CA, Clark TM, et al. Anti-tumor necrosis factor therapy in patients with refractory Takayasu's arteritis: long-term follow-up. *Ann Rheum Dis.* 2008;67(11):1567-1569.
40. Schmidt J, Kermani TA, Bacani AK, et al. Tumor necrosis factor inhibitors in patients with Takayasu arteritis: experience from a referral center with long-term followup. *Arthritis Care Res (Hoboken).* 2012;64(7):1079-1083.
41. Keystone EC. The utility of tumour necrosis factor blockade in orphan diseases. *Ann Rheum Dis.* 2004;63(Suppl 2):ii79-ii83.
42. Lamprecht P, Voswinkel J, Lilienthal T, et al. Effectiveness of TNF-alpha blockade with infliximab in refractory Wegener's granulomatosis. *Rheumatology (Oxford).* 2002;41:1303-1307.
43. Booth A, Harper L, Hammad T, et al. Prospective study of TNF-alpha blockade with infliximab in anti-neutrophil cytoplasmic antibody-associated systemic vasculitis. *J Am Soc Nephrol.* 2004;15:717-721.
44. Samuels J, Spiera R. Newer therapeutic approaches to the vasculitides: biologic agents. *Rheum Dis Clin North Am.* 2006;32:187-200.
45. 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;41:1126-1132.
46. Salvarani C, Macchioni P, Manzini C, et al. Infliximab plus prednisone or placebo plus prednisone for the initial treatment of polymyalgia rheumatica: a randomized trial. *Ann Intern Med.* 2007;146:631-639.
47. Luqmani R. Treatment of polymyalgia rheumatica and giant cell arteritis: are we any further forward? *Ann Intern Med.* 2007;146:674-676.

APPENDIX

Biologic	Mechanism of Action	Examples of Inflammatory Indications for Products*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, JIA, PsO, PsA, RA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, nr-axSpA, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, JIA, PsO, PsA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PsO, PsA, RA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: JIA, PSA, RA
		IV formulation: JIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Kineret® (anakinra SC injection)	Inhibition of IL-1	JIA^, RA
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx™ (secukinumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi™ (risankizumab-rzaa SC injection)	Inhibition of IL-23	PsO
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC
Targeted Synthetic Disease-Modifying Antirheumatic Drugs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA
Olumiant® (baricitinib tablets)	Inhibition of the JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of the JAK pathways	RA
Xeljanz®, Xeljanz XR (tofacitinib tablets, tofacitinib extended-release tablets)	Inhibition of the JAK pathways	RA, PsA, UC

* Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous; PJIA – Polyarticular juvenile idiopathic arthritis; SJIA – Systemic juvenile idiopathic arthritis; ^ Off-label use of Kineret in JIA supported in guidelines; JAK – Janus kinase.