Effective Date **3/15/2024**
Next Review Date… **3/15/2025**
Coverage Policy Number **IP0242**

Infliximab

Table of Contents

Overview 1
Medical Necessity Criteria 2
Reauthorization Criteria 8
Authorization Duration 8
Conditions Not Covered 9
Coding 9
Background 9
References 12

Related Coverage Resources

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This policy supports medical necessity review for the following infliximab products:

- Avsola™ (infliximab-axxq intravenous infusion)
- Inflectra® (infliximab-dyyb intravenous infusion)
- Infliximab intravenous infusion
- Remicade® (infliximab intravenous infusion)
- Renflexis® (infliximab-abda intravenous infusion)

Coverage for infliximab products varies across plans and requires the use of preferred products in addition to the criteria listed below. Refer to the customer's benefit plan document for coverage details.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Medical Necessity Criteria

Infliximab products are considered medically necessary when ONE of the following is met:

1. **Ankylosing Spondylitis.** Individual meets **ALL** of the following criteria:
   A. Documentation of **ONE** of the following:
      i. Failure, contraindication, or intolerance to **ONE** non-steroidal anti-inflammatory drug (NSAID)
      ii. Already tried a biologic for Ankylosing Spondylitis
   B. No documented therapeutic loss of response to infliximab product(s) up to maximum recommended dosing
   C. Medication is prescribed by, or in consultation with, a rheumatologist
   D. Preferred product criteria is met for the products listed in the below table(s)

   Dosing for Ankylosing Spondylitis. Meets **ONE** of the following regimens:
   1. Initial Therapy: up to 5 mg/kg as an intravenous infusion followed by additional doses at 2 and 6 weeks after the first infusion, then once every 6 weeks
   2. Currently Receiving an Infliximab Product: up to 10 mg/kg administered intravenously once every 4 weeks

2. **Behcet's Disease.** Individual meets **ALL** of the following criteria:
   A. Documentation of **ONE** of the following:
      i. Failure, contraindication, or intolerance to **ONE** systemic conventional therapy
      ii. Already tried a biologic for Behcet's Disease
   B. Has ophthalmic manifestations of Behcet's disease
   C. No documented therapeutic loss of response to infliximab product(s) up to maximum recommended dosing
   D. Medication is being prescribed by, or in consultation with, a rheumatologist, dermatologist, ophthalmologist, gastroenterologist, or neurologist
   E. Preferred product criteria is met for the products listed in the below table(s)

   Dosing for Behcet's Disease. Meets **ONE** of the following regimens:
   1. Initial Therapy: up to 5 mg/kg as an intravenous infusion followed by additional doses at 2 and 6 weeks after the first infusion, then once every 6 weeks
   2. Currently Receiving an Infliximab Product: up to 10 mg/kg administered intravenously once every 4 weeks

3. **Crohn's Disease.** Individual meets **ALL** of the following criteria:
   A. 6 years of age or older
   B. Documentation of **ONE** of the following:
      i. Failure, contraindication, or intolerance to **ONE** corticosteroid, OR a corticosteroid will be taken concurrently with infliximab
      ii. Failure, contraindication, or intolerance to **ONE** other conventional systemic therapy OR conventional systemic therapy will be taken concurrently with infliximab
      iii. Already tried a biologic for Crohn's Disease
      iv. Meets **ONE** of the following:
         a. Severe disease needing hospitalization
         b. Involvement of the upper GI tract
         c. Smoker
         d. Less than 40 years of age
         e. Stricturing disease
         f. Perianal disease
         g. Other enterocutaneous fistula

h. Extraintestinal manifestations (ankylosing spondylitis, pyoderma gangrenosum, erythema nodosum)
i. Previous Crohn's disease-related surgery (for example, ileocolonic resection (to reduce the chance of Crohn's disease recurrence)
j. Bowel obstruction
k. History of abscess or perforation (after healing)

C. No documented therapeutic loss of response to infliximab product(s) up to maximum recommended dosing
D. Medication is being prescribed by, or in consultation with, a gastroenterologist
E. Preferred product criteria is met for the products listed in the below table(s)

Dosing for Crohn's Disease. Meets **ONE** of the following dosing regimens:
1. Initial Therapy, up to 5 mg/kg as an intravenous infusion followed by additional doses at 2 and 6 weeks after the first infusion, then once every 8 weeks
2. Currently Receiving an Infliximab Product, up to 10 mg/kg administered intravenously once every 4 weeks

4. Graft-Versus-Host Disease. Individual meets **ALL** of the following criteria:
A. Documented failure, contraindication, or intolerance to **ONE** conventional systemic therapy (for example, corticosteroids, antithymocyte globulin, other immunosuppressants)
B. No documented therapeutic loss of response to infliximab product(s) up to maximum recommended dosing
C. Medication is being prescribed by, or in consultation with, an oncologist or hematologist
D. Preferred product criteria is met for the products listed in the below table(s)

Dosing for Graft-Versus-Host Disease. Meets the following regimen:
1. Up to 10 mg/kg intravenously once weekly

5. Hidradentitis Suppurativa. Individual meets **ALL** of the following criteria:
A. Documented failure, contraindication, or intolerance to **ONE** conventional therapy
Examples of conventional therapy: intralesional corticosteroids or systemic antibiotics
B. No documented therapeutic loss of response to infliximab product(s) up to maximum recommended dosing
C. Medication is being prescribed by, or in consultation with, a dermatologist
D. Preferred product criteria is met for the products listed in the below table(s)

Dosing for Hidradentitis Suppurativa. ONE of the following dosing regimens (1 or 2):
1. Initial Therapy, up to 5 mg/kg as an intravenous infusion followed by additional doses at 2 and 6 weeks after the first infusion, then once every 8 weeks
2. Currently Receiving an Infliximab Product, up to 10 mg/kg administered intravenously once every 4 weeks

6. Immunotherapy-Related Toxicities Associated with Checkpoint Inhibitor Therapy. Individual meets **ALL** of the following criteria:
A. Developed an immunotherapy-related toxicity other than hepatitis
B. Developed this immune-related toxicity while receiving a checkpoint inhibitor
C. Documented failure, contraindication, or intolerance to **ONE** systemic corticosteroid
D. No documented therapeutic loss of response to infliximab product(s) up to maximum recommended dosing
E. Medication is being prescribed by, or in consultation with, an oncologist, gastroenterologist, rheumatologist or ophthalmologist
F. Preferred product criteria is met for the products listed in the below table(s)

Dosing for Immunotherapy-Related Toxicities Associated with Checkpoint Inhibitor Therapy. Meets **ONE** of the following regimens:

1. Initial Therapy, up to 10 mg/kg as an intravenous infusion followed by additional doses at 2 and 6 weeks after the first infusion, then once every 4 weeks
2. Currently Receiving an Infliximab Product, up to 10 mg/kg administered intravenously once every 4 weeks

7. **Indeterminate Colitis (defined as colitis that cannot be classified with certainty as either ulcerative colitis or Crohn's disease).** Individual meets **ALL** of the following criteria:
   A. 6 years of age or older
   B. Documented failure, contraindication, or intolerance to **ALL** of the following:
      i. Systemic corticosteroid
      ii. Mesalamine
      iii. **ONE** of the following:
         a. Azathioprine
         b. 6-mercaptopurine
   C. No documented therapeutic loss of response to infliximab product(s) up to maximum recommended dosing
   D. Medication is prescribed by, or in consultation with, a gastroenterologist
   E. Preferred product criteria is met for the products listed in the below table(s)

   Dosing for Indeterminate Colitis. Meets **ONE** of the following regimens:
   1. Initial Therapy, up to 5 mg/kg as an intravenous infusion followed by additional doses at 2 and 6 weeks after the first infusion, then once every 8 weeks
   2. Currently Receiving an Infliximab Product, up to 10 mg/kg administered intravenously once every 4 weeks

8. **Non-Radiographic Axial Spondyloarthritis.** Individual meets **ALL** of the following criteria:
   A. Objective signs of inflammation, defined as **ONE** of the following:
      i. C-reactive protein (CRP) elevated beyond the upper limit of normal for the reporting laboratory
      ii. Sacroiliitis reported on magnetic resonance imaging (MRI)
   B. **ONE** of the following:
      i. Documented failure, contraindication, or intolerance to **ONE** non-steroidal anti-inflammatory drug (NSAID)
      ii. Already tried a biologic or targeted synthetic DMARD (tsDMARD) for Non-Radiographic Axial Spondyloarthritis
   C. No documented therapeutic loss of response to infliximab product(s) up to maximum recommended dosing
   D. Medication is prescribed by, or in consultation with, a rheumatologist
   E. Preferred product criteria is met for the products listed in the below table(s)

   Dosing for Non-Radiographic Axial Spondyloarthritis. Meets **ONE** of the following regimens:
   1. Initial Therapy, up to 5 mg/kg as an intravenous infusion followed by additional doses at 2 and 6 weeks after the first infusion, then once every 6 weeks
   2. Currently Receiving an Infliximab Product, up to 10 mg/kg administered intravenously once every 4 weeks

9. **Plaque Psoriasis.** Individual meets **ALL** of the following criteria:
   A. 18 years of age or older
   B. Body Surface Area (BSA) of greater than 5% OR BSA less than 5% and there is and there is involvement of the scalp, face, the palms and soles, or genitals
   C. Documentation of **ONE** of the following:

i. Failure, contraindication, or intolerance to **ONE** of the following:
    a. Topical therapy (for example, topical corticosteroids, topical vitamin D analogs, Tazorac)
    b. Systemic therapy (for example, methotrexate, cyclosporine, Soriatane)
    c. Phototherapy
ii. Already tried a biologic or targeted synthetic DMARD (tsDMARD) for Plaque Psoriasis

D. No documented therapeutic loss of response to infliximab product(s) up to maximum recommended dosing
E. Medication is prescribed by, or in consultation with, a dermatologist
F. Preferred product criteria is met for the products listed in the below table(s)

Dosing for Plaque Psoriasis. Meets **ONE** of the following regimens:
1. Initial Therapy, up to 5 mg/kg as an intravenous infusion followed by additional doses at 2 and 6 weeks after the first infusion, then once every 8 weeks
2. Currently Receiving an Infliximab Product, up to 10 mg/kg administered intravenously once every 4 weeks

10. Polyarticular Juvenile Idiopathic Arthritis (includes Juvenile Rheumatoid Arthritis, Juvenile Spondyloarthropathy/Active Sacroiliac Arthritis). Individual meets **ALL** of the following criteria:
A. No documented therapeutic loss of response to infliximab product(s) up to maximum recommended dosing
B. Medication is being prescribed by, or in consultation with, a rheumatologist
C. Preferred product criteria is met for the products listed in the below table(s)

Dosing for Polyarticular Juvenile Idiopathic Arthritis. Meets **ONE** of the following regimens:
1. Initial Therapy, up to 6 mg/kg as an intravenous infusion followed by additional doses at 2 and 6 weeks after the first infusion, then once every 8 weeks
2. Currently Receiving an Infliximab Product, up to 10 mg/kg administered intravenously once every 4 weeks

11. Psoriatic Arthritis. Individual meets **ALL** of the following criteria:
A. No documented therapeutic loss of response to infliximab product(s) up to maximum recommended dosing
B. Medication is prescribed by, or in consultation with, a rheumatologist or dermatologist
C. Preferred product criteria is met for the products listed in the below table(s)

Dosing for Psoriatic Arthritis. ONE of the following regimens:
1. Initial Therapy, up to 5 mg/kg as an intravenous infusion followed by additional doses at 2 and 6 weeks after the first infusion, then once every 8 weeks
2. Currently Receiving an Infliximab Product, up to 10 mg/kg administered intravenously once every 4 weeks

12. Pyoderma Gangrenosum. Individual meets **ALL** of the following criteria:
A. Documented failure, contraindication, or intolerance to conventional systemic therapy (for example, mycophenolate mofetil, cyclosporine or corticosteroid)
B. No documented therapeutic loss of response to infliximab product(s) up to maximum recommended dosing
C. The medication is prescribed by, or in consultation with, a dermatologist or rheumatologist
D. Preferred product criteria is met for the products listed in the below table(s)

Dosing for Pyoderma Gangrenosum. ONE of the following regimens:
1. Initial Therapy, up to 5 mg/kg as an intravenous infusion followed by additional doses at 2 and 6 weeks after the first infusion, then once every 8 weeks

2. Currently Receiving an Infliximab Product, up to 10 mg/kg administered intravenously once every 4 weeks

13. Rheumatoid Arthritis. Individual meets **BOTH** of the following criteria:
A. Documentation of **ONE** of the following:
   A. Failure, contraindication, or intolerance to **ONE** conventional synthetic disease-modifying anti-rheumatic drug (csDMARD)
   B. Already tried a biologic or targeted synthetic DMARD (tsDMARD) for Rheumatoid Arthritis
B. No documented therapeutic loss of response to infliximab product(s) up to maximum recommended dosing
C. Medication is prescribed by, or in consultation with, a rheumatologist
D. Preferred product criteria is met for the products listed in the below table(s)

Dosing for Rheumatoid Arthritis. Meets **ONE** of the following regimens:
1. Initial Therapy, up to 3 mg/kg as an intravenous infusion followed by additional doses at 2 and 6 weeks after the first infusion, then once every 8 weeks
2. Currently Receiving an Infliximab Product, up to 10 mg/kg administered intravenously once every 4 weeks

14. Sarcoidosis. Individual meets **ALL** of the following criteria:
A. Documentation of **BOTH** of the following:
   i. Failure, contraindication, intolerance to **ONE** systemic corticosteroid
   ii. Failure, contraindication, intolerance to **ONE** other immunosuppressant, unless contraindicated or intolerant
B. No documented therapeutic loss of response to infliximab product(s) up to maximum recommended dosing
C. Medication is prescribed by, or in consultation with, a pulmonologist, ophthalmologist or dermatologist
D. Preferred product criteria is met for the products listed in the below table(s)

Dosing for Sarcoidosis. ONE of the following regimens:
1. Initial Therapy, up to 5 mg/kg as an intravenous infusion followed by additional doses at 2 and 6 weeks after the first infusion, then once every 6 weeks
2. Currently Receiving an Infliximab Product, up to 10 mg/kg administered intravenously once every 4 weeks

15. Scleritis or Sterile Corneal Ulceration. Individual meets **ALL** of the following criteria:
A. Documented failure, contraindication, and intolerance to **ONE** ophthalmic or systemic immunosuppressant therapy
B. No documented therapeutic loss of response to infliximab product(s) up to maximum recommended dosing
C. Medication is prescribed by, or in consultation with, an ophthalmologist
D. Preferred product criteria is met for the products listed in the below table(s)

Dosing for Scleritis or Sterile Corneal Ulceration. Meets **ONE** of the following regimens:
1. Initial Therapy, up to 10 mg/kg as an intravenous infusion followed by up to three additional doses (for example, at 2, 6 and 8 weeks after the first infusion)
2. Currently Receiving an Infliximab Product, up to 10 mg/kg administered intravenously once every 4 weeks

16. Spondyloarthritis (non-axial disease): Reactive Arthritis (Reiter's disease) and Undifferentiated Arthritis. Individual meets **ALL** of the following criteria:
A. Individual has arthritis primarily in the knees, ankles, elbows, wrists, hands, and/or feet

B. Documentation of **ONE** of the following:
   i. Individual has had an inadequate response to **ONE** conventional synthetic disease-modifying anti-rheumatic drug (csDMARD), unless contraindicated or intolerant
   ii. Individual has already tried a biologic for non-axial spondyloarthritis
C. No documented therapeutic loss of response to infliximab product(s) up to maximum recommended dosing
D. Medication is being prescribed by, or in consultation with, a rheumatologist
E. Preferred product criteria is met for the products listed in the below table(s)

Dosing for Non-axial Spondyloarthritis. Meets **ONE** of the following dosing regimens:
1. Initial Therapy, up to 5 mg/kg as an intravenous infusion followed by additional doses at 2 and 6 weeks, then once every 6 weeks
2. Currently Receiving an Infliximab Product, up to 10 mg/kg administered intravenously once every 4 weeks

17. Still's Disease. Individual meets **ALL** of the following criteria:
A. **ONE** of the following:
   i. **BOTH** of the following:
      a. Documented failure, contraindication, or intolerance to **ONE** corticosteroid
      b. Documented failure, contraindication, or intolerance to **ONE** conventional synthetic disease-modifying antirheumatic drug (DMARD) for at least 2 months
   ii. Already tried a biologic for Still's Disease
B. No documented therapeutic loss of response to infliximab product(s) up to maximum recommended dosing
C. Medication is being prescribed by, or in consultation with, a rheumatologist
D. Preferred product criteria is met for the products listed in the below table(s)

Dosing for Still's Disease. Meets **ONE** of the following regimens:
1. Initial Therapy, up to 6 mg/kg as an intravenous infusion followed by additional doses at 2 and 6 weeks, then once every 8 weeks
2. Currently Receiving an Infliximab Product, up to 10 mg/kg administered intravenously once every 4 weeks

18. Ulcerative Colitis. Individual meets **ALL** of the following criteria:
A. 6 years of age or older
B. Documentation of **ONE** of the following:
   i. Failure, contraindication, or intolerance to **ONE** conventional systemic therapy
   ii. Already tried a biologic or targeted synthetic DMARD (tsDMARD) for Ulcerative Colitis
   iii. Has pouchitis AND has tried therapy with an antibiotic, corticosteroid enema or suppository, or mesalamine enema or suppository
C. No documented therapeutic loss of response to infliximab product(s) up to maximum recommended dosing
D. Medication is prescribed by, or in consultation with, a gastroenterologist
E. Preferred product criteria is met for the products listed in the below table(s)

Dosing for Ulcerative Colitis. Meets **ONE** of the following dosing regimens:
1. Initial Therapy, up to 5 mg/kg as an intravenous infusion followed by additional doses at 2 and 6 weeks, then once every 8 weeks
2. Currently Receiving an Infliximab Product, up to 10 mg/kg administered intravenously once every 4 weeks

19. Uveitis (includes other posterior uveitides and panuveitis syndromes). Individual meets **ALL** of the following criteria:

A. Documentation of **ONE** of the following:
   i. Failure to **ONE** ophthalmic or systemic immunosuppressant therapies, unless contraindicated or intolerant
   ii. Already tried a biologic for Uveitis
B. No documented therapeutic loss of response to infliximab product(s) up to maximum recommended dosing
C. The medication is prescribed by, or in consultation with, an ophthalmologist or rheumatologist
D. Preferred product criteria is met for the products listed in the below table(s)

Dosing for Uveitis. Meets **ONE** of the following regimens:
1. Initial Therapy, up to 10 mg/kg as an intravenous infusion followed by additional doses at 2 and 6 weeks, then once every 4 weeks
2. Currently Receiving an Infliximab Product, up to 10 mg/kg administered intravenously once every 4 weeks

Employer Plans

Product	Criteria
Remicade (infliximab) **Renflexis** (infliximab-abda)	**BOTH** of the following: 1. Documentation of **ONE** of the following: A. Trial of AND intolerance to **ONE** of the following: i. Avsola (infliximab-axxq) ii. Inflectra (infliximab-dyyb) B. One previous switch between infliximab products 2. Documented failure, contraindication, or intolerance to **ONE** other anti-tumor necrosis factor (TNF) product

Individual and Family Plans

Product	Criteria
Remicade (infliximab) **Renflexis** (infliximab-abda)	**BOTH** of the following: 1. Documentation of **ONE** of the following: A. Trial of AND intolerance to **ONE** of the following: i. Avsola (infliximab-axxq) ii. Inflectra (infliximab-dyyb) B. One previous switch between infliximab products 2. Documented failure, contraindication, or intolerance to **ONE** other anti-tumor necrosis factor (TNF) product

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Reauthorization Criteria

Infliximab is considered medically necessary for continued use when initial criteria are met AND there is documentation of beneficial response.

Authorization Duration

Initial authorization is up to 12 months.
Reauthorization is up to 12 months.

Conditions Not Covered

Any other use is considered experimental, investigational or unproven, including the following (this list may not be all inclusive):

1. **Concurrent Use with a Biologic or with a Targeted Synthetic Disease-Modifying Antirheumatic Drug (tsDMARD).** 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.

   This does NOT exclude the use of conventional synthetic DMARDs (e.g., methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with an infliximab product.

Coding

This list of codes may not be all-inclusive.

Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
J1745	Injection, infliximab, excludes biosimilar, 10 mg
Q5103	Injection, infliximab-dyyb, biosimilar, (Inflectra), 10 mg
Q5104	Injection, infliximab-abda, biosimilar, (Renflexis), 10 mg
Q5121	Injection, infliximab-axxq, biosimilar, (Avsola), 10 mg

Background

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.

- **Ankylosing Spondylitis and Non-Radiographic 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. Guidelines from the American Gastroenterological Association (AGA) [2021] include infliximab among the therapies for moderate to severe Crohn's disease, for induction and maintenance of remission.[6]

- **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.[7]

- **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.[8]

- **Rheumatoid Arthritis:** Guidelines from ACR (2021) recommend addition of a biologic or a targeted synthetic disease modifying anti-rheumatic drug (DMARD) for a patient taking the maximum tolerated dose of methotrexate who is not at target.[9]

- **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: budesonide extended-release tablets; oral or intravenous systemic corticosteroids, Entyvio® (vedolizumab intravenous infusion), Xeljanz®/XR (tofacitanib tablets/extended-release tablets), or TNFis.[10] 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 AGA (2020) recommend infliximab for moderate to severe ulcerative colitis.[12]

- **Behcet's Disease:** The European League Against Rheumatism (EULAR) recommendations (2018) include TNFis for initial or recurrent sight-threatening uveitis.[13] 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] note 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.[14]

- **Graft-Versus-Host Disease:** Guidelines from the National Comprehensive Cancer network (NCCN) [version 3.2023 – October 9, 2023] list infliximab among the agents used for steroid-refractory disease.[15]

- **Hidradenitis Suppurativa:** Guidelines from the US and Canadian Hidradenitis Suppurativa Foundations make recommendations for topical, intralesional, and systemic medical management of disease.[16] For acute lesions of all stages, antiseptic washes, short-term oral steroids, and interlesional steroids are among the recommendations. Systemic antibiotics have been a mainstay of treatment. Infliximab is a recommended therapy for moderate to severe disease.

- **Immunotherapy-Related Toxicities Associated with Checkpoint Inhibitors:** NCCN has guidelines (version 3.2023 – October 11, 2023) for Management of Immunotherapy-Related Toxicities.[17] Infliximab is recommended among the alternatives to manage steroid-refractory inflammatory arthritis, vision changes, myocarditis, pericarditis, acute kidney injury (e.g., azotemia, creatinine elevation, inability to maintain acid/base or electrolyte balance, urine output change), pneumonitis, myalgia, or myositis, and diarrhea/colitis. Additionally, the guidelines also note that infliximab should not be used to treat hepatitis associated with an immunotherapy-related toxicity.

- **Indeterminate Colitis:** Infliximab has been effective in some patients with refractory indeterminate colitis (retrospective reviews).[18,19] 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.

- **Juvenile Idiopathic Arthritis (JIA):** There are guidelines from ACR and the Arthritis Foundation for the treatment of JIA (2021) which address oligoarthritis and temporomandibular joint (TMJ) arthritis.[20] For oligoarthritis, a biologic is recommended following a trial of a conventional synthetic DMARD. In patients with TMJ arthritis, scheduled nonsteroidal anti-inflammatory drugs (NSAIDs) and/or intra-articular glucocorticoids are recommended first-line. A biologic is a therapeutic option if there is an inadequate response or intolerance. Additionally, rapid escalation to a biologic ± conventional synthetic DMARD (methotrexate preferred) is often appropriate given the impact and destructive nature of TMJ arthritis. In these guidelines, there is not a preferred biologic that should be initiated for JIA. The ACR/Arthritis Foundation Guideline for the treatment of JIA (2019) provides updated recommendations for juvenile non-systemic polyarthritis, sacroiliitis, and enthesitis.[21] 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.[22]

- **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.[14] 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). 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.

- **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.[23] 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.

- **Sarcoidosis:** The European Respiratory Society Task Force has guidelines for treatment of pulmonary, cutaneous, cardiac, and neurologic sarcoidosis.[24] Infliximab is a recommended therapy after continued disease or relapse while taking systemic corticosteroids and immunosuppressants (e.g., methotrexate, azathioprine, leflunomide, mycophenolate mofetil, hydroxychloroquine).

- **Still's Disease:** Still's disease presents in adults with features similar to those of systemic onset JIA.[25,26] In case series, infliximab has been effective in patients with Still's disease that was refractory to therapy with corticosteroids, methotrexate, azathioprine, and cyclophosphamide.[27]

Dosing Information

The recommended dose of infliximab intravenous is weight-based and varies slightly by indication.[1-3] Dosing increase, interval shortening, or changing to another therapy is generally recommended for attenuation of response. Thus, published recommendations note that the dose and interval of infliximab may be adjusted, as needed, in patients who initially respond but then lose that response.[2] Additionally, data are emerging concerning tapering of infliximab dosage in patients with inflammatory conditions who are in remission or have low disease activity. When the dose of any RA therapy is tapered, it is recommended that there be a comprehensive plan to monitor disease activity and address possible flares.

References

1. Infliximab intravenous infusion [prescribing information]. Horsham, PA: Janssen; October 2021.
2. Inflectra injection [prescribing information]. Lake Forest, IL: Hospira/Pfizer; June 2021.
3. Renflexis injection [prescribing information]. Jersey City, NJ: Samsung Bioepis/Organon; January 2022.
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. Feuerstein JD, Ho EY, Shmidt E, et al. AGA clinical practice guidelines on the medical management of moderate to severe luminal and perianal fistulizing Crohn's disease. *Gastroenterology*. 2021;160(7):2496-2508.
7. 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.
8. 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.
9. Fraenkel L, Bathon JM, England BR, et al. 2021 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatol*. 2021;73(7):1108-1123.

10. Rubin DT, Ananthakrishnan AN, Siegel CA, et al. ACG clinical guideline: ulcerative colitis in adults. *Am J Gastroenterol*. 2019;114(3):384-413.
11. Pardi DS, D'Haens G, Shen B, et al. Clinical guidelines for the management of pouchitis. *Inflamm Bowel Dis*. 2009;15(9):1424-1431.
12. 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.
13. 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.
14. 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.
15. The NCCN Hematopoietic Cell Transplantation (HCT) Clinical Practice Guidelines in Oncology (Version 3.2023 – October 9, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 9, 2023.
16. Alikhan A, Sayed C, Alavi A, et al. North American clinical management guidelines for hidradenitis suppurativa: a publication from the United States and Canadian Hidradenitis Suppurativa Foundations: Part II: topical, intralesional, and systemic medical management. *J Am Acad Dermatol*. 2019;81(1):91-101.
17. The NCCN Management of Immunotherapy-Related Toxicities Clinical Practice Guidelines in Oncology (Version 3.2023 – October 11, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed November 9, 2023.
18. Papadakis KA, Treyzon L, Abreu MT, et al. Infliximab in the treatment of medically refractory indeterminate colitis. *Aliment Pharmacol Ther.* 2003;18:741-747.
19. 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.
20. Onel KB, Horton DB, Lovell DJ, et al. 2021 American College of Rheumatology guideline for the treatment of juvenile idiopathic arthritis: therapeutic approaches for oligoarthritis, temporomandibular joint arthritis, and systemic juvenile idiopathic arthritis. *Arthritis Rheumatol.* 2022 Apr;74(4):553-569.
21. 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.
22. 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.
23. Dabade TS, Davis MD. Diagnosis and treatment of the neutrophilic dermatoses (pyoderma gangrenosum, Sweet's syndrome). *Dermatol Ther*. 2011;24(2):273-284.
24. Baughman RP, Valeyre D, Korsten P, et al. ERS clinical practice guidelines on treatment of sarcoidosis. *Eur Respir J*. 2021;58(6):2004079.
25. 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.
26. Pouchot J, Arlet JB. Biological treatment in adult-onset Still's disease. *Best Pract Res Clin Rheumatol*. 2012;26(4):477-487.
27. Kontzias A, Efthimiou P. Adult-onset Still's disease: pathogenesis, clinical manifestations and therapeutic advances. *Drugs.* 2008;68:319-337.

APPENDIX

Table 1. Approved TNFis for Targeted Indications.

	Rheumatology					Dermatology	Gastroenterology	
	RA	JIA	AS	nr-axSpA	PsA	PsO	CD	UC
Tumor Necrosis Factor Inhibitors								
Cimzia	√	--	√	√	√	√	√	--
Enbrel	√	√	√	--	√	√	--	--
Humira	√	√	√	--	√	√	√	√
Infliximab Products	√	--	√	--	√	√	√	√
Simponi Subcutaneous	√	--	√	--	√	--	--	√
Simponi Aria	√	√	√	--	√	--	--	--

TNFis – Tumor necrosis factor inhibitors; RA – Rheumatoid arthritis; JIA – Juvenile idiopathic arthritis; AS – Ankylosing spondylitis; nr-axSpA – Non-radiographic spondyloarthritis; PsA – Psoriatic arthritis; PsO – Plaque psoriasis; CD – Crohn's disease; UC – Ulcerative colitis; # Remicade, biosimilars.

Table 2. Approved IL-17, IL-23, and IL-12/23 Blockers for Targeted Indications.

	Rheumatology			Dermatology	Gastroenterology	
	Ankylosing Spondylitis	nr-axSpA	Psoriatic Arthritis	Plaque Psoriasis	Crohn's Disease	Ulcerative Colitis
Interleukin-17 Blockers						
Cosentyx	√	√	√	√	--	--
Siliq	--	--	--	√	--	--
Taltz	√	√	√	√	--	--
Interleukin-23 Blockers						
Ilumya	--	--	--	√	--	--
Skyrizi	--	--	--	√	--	--
Tremfya	--	--	√	√	--	--
Interleukin-12/23 Blockers						
Stelara Subcutaneous	--	--	√	√	√^	√^
Stelara Intravenous	--	--	--	--	√#	√#

IL – Interleukin; nr-axSpA – Non-radiographic spondyloarthritis; ^ Maintenance dosing only; # Induction dosing only.

Table 3. Approved Oral tsDMARDs for Targeted Indications.

	Rheumatology			Dermatology	Gastroenterology
	Rheumatoid Arthritis	Juvenile Idiopathic Arthritis	Psoriatic Arthritis	Plaque Psoriasis	Ulcerative Colitis
Janus Kinases Inhibitors					
Olumiant	√	--	--	--	--
Rinvoq	√	--	--	--	--
Xeljanz tablets	√	√#	√	--	√
Xeljanz oral solution	--	√#	--	--	--
Xeljanz XR	√	--	√	--	√
Phosphodiesterase Type 4 Inhibitor					
Otezla	--	--	√	√	--
Sphingosine 1-Phosphate Receptor Modulator					
Zeposia	--	--	--	--	√

tsDMARDs – Targeted synthetic disease-modifying antirheumatic drugs; # Indicated in polyarticular JIA.

Table 4. Other Approved Biologics for Targeted Indications.

	Rheumatology		
	Rheumatoid Arthritis	**Juvenile Idiopathic Arthritis**	**Psoriatic Arthritis**
Interleukin-6 Blockers			
Actemra Intravenous	√	√^	--
Actemra Subcutaneous	√	√^	--
Kevzara	√	--	--
Interleukin-1 Blocker			
Kineret	√	--	--
T-Cell Costimulation Modulator			
Orencia Intravenous	√	√#	√
Orencia Subcutaneous	√	√#	√
CD20-Directed Cytolytic Antibody			
Rituximab Intravenous Products	√	--	--

^ Indicated in polyarticular and systemic JIA; # Indicated in polyarticular JIA.