Medical Benefit Injectable Coverage Criteria

Infliximab

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Related Coverage Resources

- Immunomodulators – Oral and Subcutaneous
  (Employer Group Benefit Plans)
- Immunomodulators – Oral and Subcutaneous
  (Individual and Family Plans)

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.

Medical Necessity Criteria

Infliximab (Remicade®), infliximab-dyyb (Inflectra™), and infliximab-abda (Renflexis™) are considered medically necessary when any of the following criteria are met:

- Ankylosing spondylitis and the following:
  - Documented failure or inadequate response, contraindication per FDA label, intolerance, or not a candidate for ONE non-steroidal anti-inflammatory drug (NSAIDs)

- Crohn's disease (moderate to severe) and the following:
  - Individual is 6 years of age or older

- Graft versus host disease and the following:
  - Documented failure or inadequate response, contraindication per FDA label, intolerance, or not a candidate for systemic corticosteroid

- Hidradenitis suppurativa (moderate to severe) and all of the following:
  - Individual 18 years of age or older
  - Recurrent abscesses/inflammatory nodules and scar formation
• Failure of conventional medical management (for example, good hygiene, antibiotic therapy, and surgical incision and draining)
• Failure to 16 weeks of Humira (adalimumab) therapy

• Immune checkpoint inhibitor therapy*-related adverse event management meeting any of the following:
  o Moderate or severe diarrhea or colitis
  o Severe pneumonitis if no improvement after 48 hours of methylprednisolone
  o Severe or life-threatening renal failure/elevated serum creatinine if level remains 2-3 times above baseline after 1 week of corticosteroids
  o Life-threatening myocarditis, pericarditis, arrhythmias, or impaired ventricular function
  o Refractory/severe inflammatory arthritis not responding to corticosteroids or anti-inflammatory agents
  *Keytruda (pembrolizumab), Opivo (nivolumab), Yervoy (ipilimumab)

• Plaque psoriasis (chronic) and all of the following:
  o Individual is 18 years of age or older
  o Body surface area (BSA) of greater than 5% OR BSA less than 5% and there is involvement with the face, genitals, hands and feet (for example, nail psoriasis, palmoplantar disease), scalp, or intertriginous areas
  o Documented failure or inadequate response, contraindication per FDA label, intolerance, or not a candidate for any of the following:
    ▪ Systemic therapy (for example, methotrexate, cyclosporine, Soriatane)
    ▪ Phototherapy [narrow or broad band ultraviolet B (UVB), or psoralen plus ultraviolet A (PUVA)]
    ▪ Topical therapy (for example, coal tar, keratolytics, corticosteroids, anthralin, Dovonex, Tazorac)

• Polyarticular Juvenile Idiopathic Arthritis (PJIA) and the following:
  o Individual is 2 years of age or older

• Psoriatic arthritis and the following:
  o Documented failure or inadequate response, contraindication per FDA label, intolerance, or not a candidate for ONE disease-modifying anti-rheumatic drug (DMARD) (for example, methotrexate, leflunomide, sulfasalazine)

• Pulmonary sarcoidosis and both of the following:
  o Documented failure or inadequate response, contraindication per FDA label, intolerance, or not a candidate for corticosteroids
  o Documented failure or inadequate response, contraindication per FDA label, intolerance, or not a candidate for one immunosuppressant (for example, methotrexate, cyclophosphamide, azathioprine)

• Rheumatoid arthritis and the following:
  o Documented failure or inadequate response, contraindication per FDA label, intolerance, or not a candidate for ONE disease-modifying anti-rheumatic drug (DMARD) (for example, methotrexate, leflunomide, sulfasalazine)

• Ulcerative colitis and both of the following:
  o Individual is 6 years of age or older
  o Documented failure or inadequate response, contraindication per FDA label, intolerance, or not a candidate for at least ONE conventional therapy: (for example, aminosalicylate, corticosteroids or immunosuppressants)

• Uveitis (including intermediate, posterior and panuveitis) and the following:
  o Documented failure or inadequate response, contraindication per FDA label, intolerance, or not a candidate for conventional therapy (such as corticosteroids or immunosuppressive drugs [for example, azathioprine, cyclosporine, or methotrexate])
Coverage for infliximab varies across plans. Refer to the customer’s benefit plan document for coverage details. Where coverage requires the use of preferred products, the following criteria apply.

For Employer Group Benefit Plans and Individual and Family Plans: Inflectra (infliximab-dyyb) and Renflexis (infliximab-abda) are covered when both of the following are met:
- Documented intolerance to Remicade (infliximab) with no previous severe hypersensitivity reaction to infliximab
- For ankylosing spondylitis, Crohn’s disease, chronic plaque psoriasis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, rheumatoid arthritis, or ulcerative colitis: Documented failure or inadequate response, contraindication per FDA label, intolerance, or not a candidate (for example, fistulizing Crohn’s disease) for one other anti-tumor necrosis factor (TNF) biologic

Initial authorization is up to 12 months.

Infliximab is considered medically necessary for continued use when the initial criteria are met. Reauthorization for up to 12 months.

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.

Infliximab is considered experimental, investigational or unproven for ANY other use including the following:
- Concomitant use with any other biologic including all non-tumor necrosis factor (non-TNF) biologics, anti-TNF biologics, or oral immunomodulatory agents for example, Otezla or Xeljanz/ Xeljanz XR
- Behcet’s disease
- Granulomatosis with polyangitis
- Pyoderma gangrenosum

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

**FDA Approved Indications**

**Crohn’s Disease (CD)**
Remicade/Inflectra/Renflexis are indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn’s disease who have had an inadequate response to conventional therapy.

Remicade/Inflectra/Renflexis are indicated for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing Crohn’s disease.

**Pediatric Crohn’s Disease (CD)**
Remicade/Inflectra/Renflexis are indicated for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active Crohn’s disease who have had an inadequate response to conventional therapy.

**Ulcerative Colitis (UC)**
Remicade/Inflectra/Renflexis are indicated for reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.

**Pediatric Ulcerative Colitis (UC)**
Remicade* is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.

*Inflectra and Renflexis, biosimilars of Remicade, are not FDA approved for pediatric ulcerative colitis due to marketing exclusivity for Remicade at this time.

**Rheumatoid Arthritis (RA)**
Remicade/Inflectra/Renflexis, in combination with methotrexate, are indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis.

**Ankylosing Spondylitis**
Remicade/Inflectra/Renflexis are indicated for reducing signs and symptoms in patients with active ankylosing spondylitis.

**Psoriatic Arthritis**
Remicade/Inflectra/Renflexis are indicated for reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in patients with psoriatic arthritis.

**Plaque Psoriasis**
Remicade/Inflectra/Renflexis are indicated for the treatment of adult patients with chronic severe (i.e., extensive and/or disabling) plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate. Remicade should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician.

## Recommended Dosing

<table>
<thead>
<tr>
<th>Indication</th>
<th>FDA Recommended Dosing</th>
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<tbody>
<tr>
<td><strong>Crohn’s Disease</strong></td>
<td>The recommended dose of infliximab is 5 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter for the treatment of adults with moderately to severely active Crohn’s disease or fistulizing Crohn’s disease. For adult patients who respond and then lose their response, consideration may be given to treatment with 10 mg/kg. Patients who do not respond by Week 14 are unlikely to respond with continued dosing and consideration should be given to discontinue infliximab in these patients.</td>
</tr>
<tr>
<td>or Fistulizing Crohn’s Disease</td>
<td>The recommended dose of infliximab for children 6 years and older with moderately to severely active Crohn’s disease is 5 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks.</td>
</tr>
<tr>
<td><strong>Ulcerative Colitis</strong></td>
<td>The recommended dose of infliximab is 5 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter for the treatment of moderately to severely active ulcerative colitis.</td>
</tr>
<tr>
<td></td>
<td>The recommended dose of Remicade* for pediatric patients 6 years and older with moderately to severely active ulcerative colitis is 5 mg/kg given as an intravenous induction regimen at 0, 2, and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks.</td>
</tr>
<tr>
<td><strong>Rheumatoid Arthritis</strong></td>
<td>The recommended dose of infliximab is 3 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 3 mg/kg every 8 weeks thereafter for the treatment of moderately to severely active rheumatoid arthritis. Infliximab should be given in combination with methotrexate. For patients who have an</td>
</tr>
<tr>
<td>Indication</td>
<td>FDA Recommended Dosing</td>
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</tr>
<tr>
<td>Ankylosing Spondylitis</td>
<td>The recommended dose of infliximab is 5 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 6 weeks thereafter for the treatment of active ankylosing spondylitis.</td>
</tr>
<tr>
<td>Psoriatic Arthritis</td>
<td>The recommended dose of infliximab is 5 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter if infliximab can be used with or without methotrexate.</td>
</tr>
<tr>
<td>Plaque Psoriasis</td>
<td>The recommended dose of infliximab is 5 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter.</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>The recommended dose of infliximab is 5 mg/kg given as an intravenous infusion followed with additional similar doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter.</td>
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**Drug Availability**

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Drug Availability</th>
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<tbody>
<tr>
<td>Inflectra</td>
<td>Inflectra is supplied in 100 mg of infliximab-dyyb in a 20 mL vial for intravenous infusion</td>
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<tr>
<td>Remicade</td>
<td>Remicade IV injection is supplied in individually-boxed single-use vials in 100 mg infliximab in a 20 mL vial.</td>
</tr>
<tr>
<td>Renflexis</td>
<td>Each Renflexis (infliximab-abda) for Injection 100 mg vial is individually packaged in a carton. Each single dose vial contains 100 mg of infliximab-abda for final reconstitution volume of 10 mL.</td>
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**Background**

**Pharmacology**

Anti-TNF agents bind specifically to TNF-alpha and block its interaction with the cell surface TNF receptors. TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. TNF promotes the synthesis of other proinflammatory cytokines, stimulates endothelial cells to express adhesion molecules that attract leukocytes into affected joints, accelerates the production of metalloproteinases, and inhibits the synthesis of cartilage proteoglycans. Increased concentrations of TNF also are found in psoriatic plaques. TNF blockers modulate responses that are induced or regulated by TNF, including expression of adhesion molecules, serum concentrations of matrix metalloproteinase, and serum concentrations of cytokines. Two distinct receptors for TNF (TNFRs), a 55 kilodalton protein (p55) and a 75 kilodalton protein (p75), exist naturally as monomeric molecules on cell surfaces and in soluble forms. Biological activity of TNF is dependent upon binding to either cell surface of TNFR.

**Professional Societies/Organizations**

**Ankylosing Spondylitis**

**Assessment in SpondyloArthritis International Society (ASAS)/EULAR**

The Assessment in SpondyloArthritis International Society (ASAS)/EULAR published guidelines for the treatment of Ankylosing Spondylitis. These guidelines recommends for axial spondyloarthritis that NSAIDs be used first-line, and for selected patients that glucocorticoids and sulfasalazine are appropriate. Guidelines further state that biologics be considered in patients with high disease activity despite the use of conventional treatments, with the current practice being a TNF inhibitor. If the TNF inhibitor fails, the guidelines recommend switching to another TNF inhibitor or an IL-17 antagonist could be considered (van der Heijde 2017).  

**American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network 2015 Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis**

The 2015 recommendations state that in active Ankylosing Spondylitis, NSAIDS are strongly recommended over no treatment (evidence: low quality). In adults with active Ankylosing Spondylitis despite treatment with an...
NSAID, treatment with TNF inhibitor is strongly recommended over no treatment with TNF inhibitor (evidence: moderate quality). No particular TNF inhibitor is preferred, except for patients with concomitant inflammatory bowel disease or recurrent iritis (evidence: moderate quality). Panel stated in patients with Ankylosing Spondylitis and inflammatory bowel disease or frequently recurrent iritis that treatment with infliximab or adalimumab should be preferred over etanercept. In active nonradiographic axial spondyloarthritis despite treatment with NSAIDs, the guidelines recommend treatment with TNF inhibitors over no treatment with TNF inhibitors (evidence: moderate quality). Guidelines do not address interleukin therapy. (Ward, 2016)

Crohn’s Disease

American College of Gastroenterology (ACG) Clinical Guideline: Management of Crohn’s Disease in Adults
Recommendations for immunomodulatory therapies are as follows:

Moderate to severe disease/moderate to high risk disease
- Infliximab, adalimumab, or certolizumab pegol are recommended in those who have not responded to treatment with a corticosteroid or an immunosuppressive agent
- Use of infliximab concomitantly with an immunomodulator is more efficacious than monotherapy with either agent in individuals naïve to these medications
- Vedolizumab with or without use of an immunomodulator should be considered for induction of remission in individuals with moderately to severely active Crohn’s disease with evidence of active disease
- Natalizumab should be a consideration for induction of symptomatic response and remission in active Crohn’s disease
- Natalizumab should be used to maintain natalizumab-induced remission of Crohn’s disease only if antibodies are negative to John Cunningham (JC) virus
- Ustekinumab should be used in individuals with moderate to severe Crohn’s disease who have not responded to corticosteroids, thiopurines, methotrexate or anti-TNF inhibitors, or who are anti-TNF naïve

Severe/fulminant disease
- Infliximab, adalimumab, and certolizumab pegol may be used to treat severely active Crohn’s disease
- Infliximab may be used to treat fulminant Crohn’s disease

Perianal/fistulizing disease
- Infliximab should be considered for treatment of perianal fistulas in Crohn’s disease
- Infliximab should be a consideration for treatment of enterocutaneous and rectovaginal fisulas in Crohn’s disease
- Adalimumab and certolizumab pegol should be a consideration to treat perianal fistulas in Crohn’s disease

Maintenance Therapy of Luminal Crohn’s Disease
- Anti-TNF therapy should be used for maintenance therapy of anti-TNF induced remission (specifically Infliximab, adalimumab and certolizumab pegol)
- Although monotherapy with anti-TNFs is efficacious in maintaining anti-TNF induced remissions, consideration should be given to concomitant use with azathioprine/6-mercaptopurine or methotrexate due to the risk for immunogenicity and loss of response
- Vedolizumab therapy should be utilized to maintain vedolizumab-induced remissions of Crohn’s disease
- Natalizumab therapy should be a consideration for maintenance of natalizumab-induced of remissions in Crohn’s disease if John Cunningham (JC) virus is negative
- Ustekinumab therapy should be used to maintain ustekinumab-induced remissions of Crohn’s disease

(Lichtenstein, 2018)
American Gastroenterological Association (AGA) Guideline on the Use of Thiopurines, Methotrexate, and Anti–TNF-α Biologic Drugs for the Induction and Maintenance of Remission in Inflammatory Crohn’s Disease

The AGA provides recommendations for the induction and maintenance of remission in inflammatory Crohn’s disease. Specifically addressing biologic therapy, the recommendations are as follows:

**Induction of Remission** in patients with moderately to severely active Crohn’s disease:

- Anti-TNF biologics are recommended.
- If monotherapy is utilized, anti-TNF biologics are preferred over thiopurine monotherapy.
- If combination therapy is utilized, anti-TNF biologics combined with thiopurines is the suggested regimen.

**Maintenance of Remission**

- It is recommended to use an anti-TNF biologic to maintain remission which was induced by corticosteroids or an anti-TNF biologic.
- The AGA is neutral regarding use of combination therapy of an anti-TNF biologic plus a thiopurine compared to either class alone to maintain remission which was achieved by use of a combination of these classes. (Terdiman, 2013)

European Evidence-based Consensus (ECCO) on the Diagnosis and Management of Crohn’s Disease

The third ECCO evidence based consensus group stated guidelines were, in part, revisited in order to recognize the Crohn’s Disease indication for vedolizumab along with its clinical data. Several recommendations were provided by the ECCO guidelines on the use of vedolizumab in the treatment of Crohn’s Disease. They are as follows:

- Moderately active localised ileocaecal Crohn’s disease: Treat with budesonide or with systemic corticosteroids; Anti-TNFs could be used as an alternative for those patients that are steroid-refractory or intolerant; In patients refractory to steroids or Anti-TNFs, vedolizumab is an alternative (Gomollon, 2017)
- Active colonic Crohn’s Disease: Treat with systemic corticosteroids; AntiTNFs is appropriate in those who have relapsed; In patients refractory to steroids or AntiTNFs, vedolizumab is an alternative (Gomollón, 2017)

If remission has been achieved with the combination then maintenance with the same regimen is recommended. Therefore, maintenance treatment with vedolizumab is appropriate in patients achieving remission with vedolizumab. (Gomollón, 2017)

**Hidradenitis Suppurativa**

European guidelines for hidradenitis suppurativa and acne inversa suggest surgery or laser procedures for locally recurring lesions. In cases where lesions are more widespread, treatment options include medical monotherapy or in combination with more radical surgery. Medical therapies mentioned include antibiotics (clindamycin plus rifampicine, tetracycles), acitretin and biologics (adalimumab, infliximab). (Zouboulis, 2014)

In a randomized, double-blind, placebo-controlled, crossover trial of 38 individuals, infliximab (5 mg/kg on weeks 0,2, and 6) was compared to placebo infusions. An open-label phase followed, where individuals in the infliximab arm had maintenance infusions of infliximab at weeks 14 and 22, while the individuals in the placebo arm were allowed the option to receive infliximab to receive infliximab per the same treatment protocol. Evaluation at week 8 did not demonstrate a significant difference between the infliximab and placebo arms for the primary endpoint of a greater than or equal to 50 percent decrease in an unvalidated disease severity score. Patient quality of life, pain and physician global assessments did demonstrate statistically significant improvements in the infliximab group. (Grant, 2010).

**Immune Checkpoint Inhibitor Related Adverse Events**

According to the National Comprehensive Cancer Network (NCCN), infliximab has frequently been utilized to treat immune related adverse events (irAEs) which occur during immune checkpoint inhibitor therapy (ICI), and have failed to respond to steroid treatment. If severe irAEs are resistant to 48 to 72 hours of steroid therapy, timely initiation (i.e., at 72 hours) of anti-TNFα therapy is a reasonable approach. Most often, one dose of a
TNFα blocker is sufficient, however a second dose may be necessary and should be administered 2 weeks after the initial dose. Currently, there is no specific information available in regards to the appropriate duration of the TNFα blocker therapy. The guideline mentions that the TNFα blockers are very effective in the treatment of immune-related colitis and inflammatory arthritis. (NCCN, 2018)

**Juvenile Idiopathic Arthritis**

American College of Rheumatology (ACR) 2013 Update of the 2011 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 (Ringold, 2013)

**Systemic JIA Treatment Recommendations:**

**Initial treatment in patients with the following: active systemic features and varying degrees of synovitis**

- Systemic monotherapy with a glucocorticoid (either oral or intravenous) is recommended for a maximum of two weeks for patients with an MD global < 5 and Active Joint Count > 4 and for all patients with an physician global assessment (MD) ≥ 5 irrespective of the Active Joint Count.
- Initiating monotherapy with an NSAID in a patient without prior treatment is recommended as an option for patients with an MD global < 5 irrespective of the Active Joint Count.

**Treatment in patients with active systemic features and varying degrees of synovitis, with continued disease activity**

- Glucocorticoid monotherapy is recommended as a treatment option after failure of NSAID monotherapy for patients with an MD global < 5 and Active Joint Count > 0 and for patients with an MD global ≥ 5 (irrespective of the Active Joint Count).
- Intraarticular glucocorticoid injection is recommended as adjunct therapy at any time.
- Methotrexate (or leflunomide) is recommended for patients with an MD global < 5 and Active Joint Count > 0 after treatment with the following: glucocorticoid monotherapy, tocilizumab, or an IL-1 inhibitor. Methotrexate (or leflunomide) is recommended for patients with an MD global ≥ 5 and Active Joint Count > 0 (only after a trial of an IL-1 inhibitor or tocilizumab).
- Initiation with a TNF inhibitor is recommended for patients with Active Joint Count > 4 that is irrespective of the MD global after a trial of an IL-1 inhibitor or tocilizumab.
- Initiation with a TNF inhibitor is recommended for patients with Active Joint Count > 0 irrespective of the MD global after a trial of both an IL-1 inhibitor and tocilizumab sequentially.
- The use of a TNF inhibitor for patients with an MD global <5 and Active Joint Count = 0 is inappropriate, with the following exception: in patients who had tried both an IL-1 inhibitor and tocilizumab sequentially or a DMARD plus either an IL-1 inhibitor or tocilizumab (in which case it is uncertain).
- The use of a TNF inhibitor for patients with an MD global ≥ 5 and Active Joint Count = 0 is inappropriate, with the following exception: in patients who had tried an IL-1 inhibitor or tocilizumab (in which case it is uncertain).

**Initial treatment in patients without active systemic features and varying degrees of synovitis**

- Intraarticular glucocorticoid injection is recommended as an initial treatment in patients with Active Joint Count ≤ 4.
- Initiation of methotrexate (or leflunomide) is recommended in patients with Active Joint Count > 4.
- Initiation of NSAID monotherapy in patients without prior treatment for a maximum of one month is recommended as a treatment approach for patients with Active Joint Count > 0. Note: Continuing NSAID monotherapy for longer than two months for patients with continued disease activity is inappropriate.

**Treatment in patients without active systemic features and varying degrees of synovitis, with continued disease activity**

- The use of methotrexate (or leflunomide) is recommended as a treatment option for Active Joint Count > 0 following treatment with the following: intraarticular injection, NSAID monotherapy, an IL-1 inhibitor, or tocilizumab.
- Initiation of a TNF inhibitor is recommended in patients with Active Joint Count > 0 after treatment with the following: methotrexate (or leflunomide), anakinra, or tocilizumab.
When continued disease activity is present after DMARD and NSAID use, the following are options when continued therapy is required: Abatacept, Anakinra, TNF inhibitor, Tocilizumab

Initial treatment in patients with features concerning for MAS (macrophage activation syndrome)

- The use of systemic glucocorticoid monotherapy (administered by either oral or IV) is also recommended as a therapeutic option for patients with features concerning for MAS.

Psoriasis and Psoriatic Arthritis
American Academy of Dermatology (AAD)

The AAD updated their 2008 published guidelines for the care and treatment of psoriasis and psoriatic arthritis in July 2011. Psoriasis severity is defined by both the extent of body surface area (BSA) involvement (<5% considered mild, >5% but <10% moderate, and >10% severe), and the involvement of the hands, feet, facial, or genital regions. The majority of psoriasis patients have involvement defined as less than 5% BSA and can effectively treated with topical agents. Psoriasis patients who are candidates for ultra-violet based or systemic therapy (which include oral and biologic agents) have more significant disease, defined as affecting more than 5% of the BSA, or may have less than 5% BSA affected but have psoriasis in vulnerable areas such as the face, genitals, hands and feet (palmoplantar disease), scalp, or intertriginous areas and have disease that adversely affects their quality of life.

Despite the introduction of current and future biologic agents, topical medications, phototherapy, photochemotherapy, and traditional systemic drugs continue to play an essential role in the therapeutic armamentarium of psoriasis. Topical therapies are the mainstay for mild disease either as monotherapy or combination therapy, and are also commonly used in conjunction with phototherapy, traditional systemic agents, or biologic agents for moderate to severe disease. Phototherapy, photochemotherapy, and traditional systemic agents are generally used for individuals with moderate or severe disease and in situations in which topical therapy is ineffective or otherwise contraindicated. Phototherapy and photochemotherapy are effective and economical without many of the potential toxicities of traditional and biologic systemic therapies. However, inconvenience, lack of availability, and reimbursement issues do limit their feasibility, with home ultraviolet (UV) phototherapy an alternative for the appropriate patient. In general, traditional systemic agents (methotrexate [MTX], acitretin, cyclosporine, and others) have been available far longer than biologics (MTX was approved for psoriasis in 1971), with short- and long-term toxicity profiles that are well known from clinical practice in spite of the absence of formal long-term studies in patients with psoriasis. Traditional systemic agents are given orally (MTX may also be given by injection) and are also less expensive than injectable biologic agents. Biologic agents, including adalimumab, etanercept, and infliximab, are routinely used for moderate to severe psoriasis when one or more traditional systemic agents fail to produce an adequate response, are not tolerated because of adverse effects, or are unsuitable because of the presence of comorbidities.

For patients with moderate to severe PsA, MTX, TNF-alfa blockade, or the combination of these therapies is considered first-line treatment. However, it is appropriate to initiate MTX treatment for patients with moderate to severe PsA who have no contraindications to MTX therapy. If after 12 to 16 weeks of MTX therapy with appropriate dose escalation there is minimal improvement in the signs and symptoms of PsA, it is very appropriate to either add or switch to a TNF-alfa inhibitor, with all of the TNF-alfa inhibitors approved for PsA (adalimumab, etanercept, golimumab, and infliximab) being equally reasonable choices. Because of the lack of sufficient data, however, it is difficult for the clinician to make definitive recommendations regarding the proper sequence or duration of therapies that should be used to treat patients with moderate to severe PsA. (Menter, 2008; Menter, 2009[a]; Menter, 2009[b]; Menter, 2010; Menter, 2011)

European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update

Refer to guidelines for Strength of Evidence details.

EULAR recommendations for treatment in Psoriatic Arthritis patients

- NSAIDs may be used to relieve musculoskeletal signs and symptoms (Strength of Evidence:1b, A).
- In active disease (particularly including the following: numerous swollen joints, structural damage in the presence of inflammation, high erythrocyte sedimentation rate/C-reactive protein and/or clinically relevant extraarticular manifestations), treatment with DMARDs (methotrexate, sulfasalazine, or leflunomide) should
be considered (Strength of Evidence: 1b, B) at an early stage (Strength of Evidence: 3, B), with MTX given priority for patients with skin involvement (Strength of Evidence: 1b, B).

- Local corticosteroid injections should be considered as adjunctive therapy (Strength of Evidence: 3b, C); systemic glucocorticoids may be used with caution at the lowest effective dose (Strength of Evidence: 4, C).

- In patients with an inadequate response to at least one synthetic DMARD, therapy with a biologic, which is usually a TNF inhibitor, should be started (Strength of Evidence: 1b, B).

- In patients with peripheral arthritis and an inadequate response to at least one synthetic DMARD, in whom TNF inhibitors are not appropriate (for example, demyelinating disease), biologic DMARDs targeting IL12/23 or IL17 pathways may be considered (Strength of Evidence: 1b, B).

- In patients with peripheral arthritis and an inadequate response to at least one synthetic DMARD, in whom biologic DMARDs are not appropriate, a targeted synthetic DMARD such as a PDE4- inhibitor may be considered (Strength of Evidence: 1b, B).

- In patients with active enthesitis or dactylitis and insufficient response to either NSAIDs or corticosteroid injections, biologics should be considered. The current practice being the use of a TNF inhibitor (Strength of Evidence: 1b, B).

- In patients with predominantly axial disease which is active and has insufficient NSAID response, a biologic should be considered. The current practice being the use a TNF inhibitor (Strength of Evidence: 1b, B).

- In patients who have failed to respond to biologics, switching to another biologic should be considered. This includes switching between TNF inhibitors (Strength of Evidence: 1b, B). (Gossec, 2016; Ramiro, 2016)

**Group for Research and Assessment of Psoriasis and Psoriatic Arthritis**

The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) provides recommendations for the treatment of Plaque Psoriasis which includes the following: topical therapies, phototherapy, DMARDs, antiTNFs, IL-12/23 inhibitors, IL-17 inhibitors, and PDE-4 inhibitors. The GRAPPA recommendations for Psoriatic Arthritis vary based on the domain which is involved: peripheral arthritis, axial disease, enthesitis, dactylitis, skin, and nails. (Coates, 2016)

Treatment for psoriatic arthritis is based on peripheral or axial disease and prior therapies. Recommendations include DMARDs, NSAIDs, simple analgesics, antiTNFs, IL-12/23 inhibitors, or PDE-4 inhibitors. (Coates, 2016)

Treatment for nail disease in psoriatic arthritis is based on data from the psoriasis clinical studies. For mild disease, treatment options could include topical agents, corticosteroid injections or nonbiologic DMARDs. For moderate to severe nail psoriasis disease, GRAPPA recommends antiTNFs agents based on available data. In addition, GRAPPA further recommends that ustekinumab and IL-17 inhibitors should be considered alternative biologic therapy to antiTNFs. (Coates, 2016)

**Rheumatoid Arthritis**

*American College of Rheumatology (ACR) 2015 Guideline for the Treatment of Rheumatoid Arthritis*

In the ACR guidelines, anti–tumor necrosis factor (anti-TNF) biologics include the following: Cimzia (certolizumab), Enbrel (etanercept), Humira (adalimumab), Remicade (infliximab), and Simponi (golimumab). Non-TNF biologics include the following: Actemra (tocilizumab), Orencia (abatacept), and Rituxan (rituximab). DMARD agents include the following: methotrexate, leflunomide, sulfasalazine, and hydroxychloroquine (excludes azathioprine, cyclosporine, minocycline, and gold).

### Early disease recommendations (defined as less than 6 months)

For patients with low disease activity and in those who have not taken a DMARD, the guidelines recommend to use DMARD monotherapy (Methotrexate preferred) over double therapy or triple therapy (Recommendation: strong; Level of evidence: Low). If the disease activity remains moderate or high despite monotherapy with a DMARD, use combination DMARDs or use a TNF inhibitor or a non-TNF inhibitor biologic (all options are with or without methotrexate and given in no preference order) rather than continuing monotherapy with a DMARD (Recommendation: strong; Level of evidence: Low). If the disease activity remains moderate or high despite DMARDs, the guidelines suggest use of monotherapy with a TNF inhibitor over monotherapy with tofacitinib (Level of evidence: Low) or use a TNF inhibitor with methotrexate over tofacitinib with methotrexate (Level of evidence: Low).

### Established disease recommendations (defined as greater than 6 months)
For patients with low disease activity and those who have not taken a DMARD, the guideline recommends use of monotherapy with a DMARD (methotrexate preferred) over a TNF inhibitor (Recommendation: Strong; Level of evidence: Low). If the disease activity remains moderate or high despite monotherapy with a DMARD, use combination traditional DMARDs or add a TNF inhibitor or a non-TNF inhibitor biologic (all options are with or without methotrexate and given in no preference order) rather than continuing monotherapy with a DMARD (Recommendation: Strong; Level of evidence: Moderate to very low). If the disease activity remains moderate or high despite TNF inhibitor in patients who are not currently on a DMARD, add one or two DMARDs to a TNF inhibitor rather than continuing monotherapy with a TNF inhibitor (Level of evidence: High).

Conditional recommendations for established RA disease:
- If the disease activity remains moderate/high despite the use of non-TNF biologic, use another non-TNF biologic (with or without methotrexate) over tofacitinib (with or without methotrexate) (Level of evidence: Very low).
- If the disease activity remains moderate/high despite use of multiple (defined as ≥2) sequential TNF inhibitors, use tofacitinib (with or without methotrexate) over another TNF inhibitor (with or without methotrexate) if the use of a non-TNF biologic is not a treatment option (Level of evidence: Low).
- If the disease activity remains moderate/high despite use of TNF inhibitor and at least one non-TNF biologic, the guideline recommends to first use another non-TNF biologic (with or without methotrexate) over tofacitinib or use tofacitinib (with or without methotrexate) over another TNF inhibitor agent (Level of evidence: Very low).

Recommendations for specific high-risk conditions:
- Congestive Heart Failure (CHF): ACR guidelines recommend using combination DMARDs or a non-TNF biologic agent or tofacitinib over TNF inhibitors (conditional recommendation; Level of evidence: Moderate to very low). If there is CHF worsening on a current TNF inhibitor, ACR recommends use of a combination DMARD or non-TNF biologic or tofacitinib over another TNF inhibitor (conditional recommendation; Level of evidence: Very low).
- Previously treated lymphoproliferative disorder: ACR guidelines recommend using rituximab over TNF inhibitor (Recommendation: Strong; Level of evidence: Very low) or use combination DMARD or abatacept or tocilizumab over TNF inhibitor (conditional recommendation; Level of evidence: Very low).
- Previous serious infection: ACR guidelines recommend using combination DMARD over TNF inhibitor or use abatacept over TNF inhibitor (conditional recommendation; Level of evidence: Very low).

European League Against Rheumatism (EULAR): Management Of Rheumatoid Arthritis With Synthetic And Biological Disease-Modifying Antirheumatic Drugs: 2013 Update
This EULAR guideline recommends that methotrexate should be used as part of a first treatment strategy in active rheumatoid arthritis and, if methotrexate is contraindicated/not tolerated, treatment with sulfasalazine or leflunomide be considered. In patients with inadequate response to methotrexate and/or other conventional synthetic DMARDs, biologic DMARDs (TNF inhibitors, abatacept or tocilizumab) should be started with methotrexate. The guideline states that if the patients fails the first biologic DMARD, consider treatment with another biologic DMARD; if the first TNF inhibitor therapy has failed, the patient may receive another TNF inhibitor or a biological agent that has different mechanism of action. (Smolen, 2014)

European League Against Rheumatism: The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation

Considerations for Pregnancy:
- Biologic DMARDs (such as the following: rituximab, anakinra, tocilizumab, abatacept, and ustekinumab) have limited documentation on safe use in pregnancy. Therefore, should be replaced before conception by other medication. They should be used during pregnancy only when there are no other pregnancy compatible drug that can effectively control maternal disease (Grade of recommendation: D).
- Continuation of TNF inhibitors during the first part of pregnancy should be considered among the biologic DMARDs. Two agents, etanercept and certolizumab, may be considered for use throughout pregnancy due to low rate of transplacental passage (Grade of recommendation: B).
Considerations for Lactation:

- Biologic DMARDs with no data on breast feeding (such as the following: rituximab, anakinra, ustekinumab, tocilizumab, and abatacept) should be avoided during lactation if other therapy is available to control the disease. Lactation should not be discouraged when using these agents, if no other options are available, based on the pharmacological properties of biologic DMARDs. (Götestam Skorpen, 2016)

- For infliximab, adalimumab, etanercept, and certolizumab, there has been shown a low transfer to breast milk. The continuation of TNF inhibitors should be considered as compatible with breast feeding (Grade of recommendation: D). (Götestam Skorpen, 2016)

Ulcerative Colitis

American College of Gastroenterology (ACG) Ulcerative colitis practice guidelines in adults: American College Of Gastroenterology, Practice Parameters Committee

ACG guidelines for ulcerative colitis recommend the use of infliximab for all forms of the disease. These guidelines were developed prior to approval of adalimumab and golimumab for the disease. Goals of treatment are induction and maintenance of remission of symptoms to provide an improved quality of life, reduction in need for long-term corticosteroids, and minimization of cancer risk. (Kornbluth, 2010) The recommendations are as follows:

Management of Mild-Moderate Distal Colitis:

- First-line therapy includes aminosalicylates, topical mesalamine, or topical steroids (topical mesalamine agents are superior to topical steroids or oral aminosalicylates) where combination oral and topical aminosalicylates are more effective than either alone
- Patients refractory to oral aminosalicylates or topical corticosteroids may find mesalamine enemas or suppositories effective
- Patients refractory to all of the above agents in maximal doses or those systemically ill may require treatment with oral prednisone in doses up to 40–60 mg per day or infliximab with an induction regimen of 5 mg/kg at weeks 0, 2, and 6

Maintenance of Remission in Distal Disease:

- Mesalamine enemas and compounds, sulfasalazine, and balsalazide are effective (combination oral and topical mesalamine is more effective than either one alone)
- Thiopurines (6-mercaptopurine [6-MP] or azathioprine) and infliximab, but not corticosteroids, are effective when all the other treatments fail

Mild-Moderate Extensive Colitis: Active Disease:

- Oral sulfasalazine or an aminosalicylate
- Oral steroids for those refractory to oral aminosalicylates in combination with topical therapy or symptoms that demand rapid improvement
- 6-MP and azathioprine when there is no response to oral steroids
- Infliximab for patients who are steroid refractory or steroid dependent despite adequate doses of a thiopurine or who are intolerant of these medications

Mild-Moderate Extensive Colitis: Maintenance of Remission:

- Sulfasalazine, olsalazine, mesalamine, and balsalazide are all effective in reducing relapses
- Azathioprine or 6-MP may be useful as steroid-sparing agents for steroid-dependent patients and for maintenance of remission not adequately sustained by aminosalicylates
- Infliximab is effective in maintaining improvement and remission in the patients responding to the infliximab induction regimen

Management of Severe Colitis:

- Infliximab 5 mg/kg if urgent hospitalization is not necessary and patient is refractory to maximal oral prednisone, oral aminosalicylate drugs, and topical medications
- Infliximab may be effective in avoiding colectomy in patients failing IV steroids (long-term efficacy unknown in this setting) (Kornbluth, 2010)
Biosimilars

According to the FDA, a biosimilar is a biological product that is highly similar to and has no clinically meaningful differences from an existing FDA-approved reference product. There may be minor differences in clinically inactive components of the product. (FDA, 2017)

In the ACR guidelines for treatment of Crohn’s disease, the organization states that biosimilar forms of infliximab and adalimumab effectively treat moderate to severe Crohn’s disease and may be used in both initial induction and maintenance phases of treatment. Furthermore, the guideline mentions the current lack of evidence supporting the safety and efficacy of changing from one biosimilar to another of the same biosimilar molecule in individuals who have stable disease and are in maintenance phase (Lichtenstein, 2018). According to The Task Force on the Use of Biosimilars to Treat Rheumatological Disorders, participation by prescribers and patients is important in the decision to switch between biosimilars (Kay, 2018). In addition, studies to determine biosimilarity between infliximab and infliximab-dyyb found no meaningful differences when treating individuals with rheumatoid arthritis and psoriatic arthritis. (Park, 2013; Park, 2016; Park, 2017; Yoo, 2013; Yoo, 2016; Yoo, 2017). Likewise, in other rheumatoid arthritis studies, no meaningful differences were detected between infliximab and infliximab-abda (Choe, 2017; Shin, 2015).

The American Board of Internal Medicine’s (ABIM) Foundation Choosing Wisely® Initiative:
The American College of Rheumatology Choosing Wisely® (2013) recommends a 3 month trial of methotrexate (or another conventional non-biologic DMARD) unless contraindicated or other exceptions (e.g., high disease activity and poor prognostic features) before initiating biologic therapy for rheumatoid arthritis.

Centers for Medicare & Medicaid Services - National Coverage Determinations (NCDs)
There are no CMS National Coverage Determinations for infliximab.

Clinical Efficacy

Ankylosing Spondylitis (reactive arthritis and undifferentiated spondyloarthropathy)
Reacto arthritis is an inflammatory arthropathy which happens in response to several characteristic infections; with typical involvement including peripheral oligoarticular arthritis generally prominent in the lower extremities and usually accompanied by sacroiliitis. Undifferentiated arthritis is used to describe inflammatory arthritis which do not belong into any known category. These patients usually have rheumatoid factor negative mono or oligoarthritis that resembles Reactive Arthritis, however it is absent of an infection. (Meador, 2002). A few case series exist for adalimumab, etanercept, and infliximab in Reactive Arthritis patients. (Flagg, 2005; Meyer 2011) Their use is supported by their effectiveness in the treatment of other spondyloarthropathies, including axial and peripheral SpA and the various forms of psoriatic arthritis. (Yu, 2016)

Crohn’s Disease
Van Assche et al published results of a prospective, randomized switch trial. The trial evaluated the effect of switching to adalimumab in patients with Crohn’s disease controlled by maintenance infliximab. The results stated that elective switching of a Crohn’s disease patient from infliximab to adalimumab is associated with the loss of efficacy and tolerance within one year. The data suggests that patients who have achieved a sustained response with infliximab should be maintained on infliximab and not switched to an alternative anti TNF agent because switching in this situation is associated with worse clinical outcomes. (Van Assche, 2012)

Singh et al and Hazlewood et al published the results of two network meta-analysis providing comparative efficacy data of biologic therapy in biologic-naïve Crohn disease patients. The results stated that infliximab and adalimumab but not certolizumab were more likely to induce remission. However, in the absence of head to head trials comparing these agents, the confidence of these results are low and future comparative studies are needed. (Singh, 2014; Hazlewood, 2015)

Plaque Psoriasis: Demyelinating disorders
In a review of demyelinating disorders secondary to tumor necrosis factor (TNF)- inhibitor use in psoriasis, the incidence in clinical trials was found to be exceedingly rare. For example, of 6990 individuals who received etanercept there was a single reported case of multiple sclerosis. There are a few case reports, outside of clinical trials, of incidents of demyelinating disorders secondary to use of tumor necrosis factor-inhibitors. The
authors state that TNF- inhibitors are not recommended when there is a history of a demyelinating disorder. (Zhu, 2016)

Drug labels approved by the FDA for the TNF-inhibitors include language to exercise caution in individuals with preexisting or recent-onset of demyelinating disorders and to consider discontinuation if any demyelinating disorder occurs.

**Rheumatoid Arthritis**

**Clinical Efficacy: Comparative Trials**

**TNF versus non-TNF Biologic**

A 52 week multicenter, pragmatic, open-label randomized clinical trial evaluated non–TNF targeted biologic agent versus a second Anti-TNF to treat Rheumatoid Arthritis in patients with an insufficient response to a first Anti-TNF agent. Patients were randomly assigned 1:1 to receive a non-TNF or an anti-TNF that was different from the previous treatment. The non-TNF could be: (1) abatacept: 500 to 1000 mg IV, dosed according to the patient’s weight, every 14 days until week 4 and once monthly thereafter, (2) Rituximab: 1 g infusion IV followed by another 2 weeks later, (3) tocilizumab: 8mg/kg monthly IV. The Anti-TNF (that differed from their initial treatment) could be: (1) adalimumab: 40 mg SQ every 14 days, (2) certolizumab: 400 mg SQ every 14 days until week 4, then 200mg every 14 day, (3) Etanercept: 50 mg SQ every 7 days, (4) infliximab: 3 mg/kg IV initially (with the possibility of ascending doses at weeks 2 and 6 and every 8 weeks thereafter). At week 24, 69% in the non-TNF group and 52% in the second anti-TNF group achieved a EULAR response which was defined as "good" or "moderate". The authors concluded that in patients with rheumatoid arthritis that were previously treated with anti-TNFs but with an inadequate primary response, non-TNFs were more effective in achieving a good or moderate disease activity response at 24 weeks than was the 2nd anti-TNF. (Gottenberg, 2016)

**Off-Label Uses**

AHFS Drug Information 2019 Edition does not support any off-label uses of infliximab.

**Graft versus Host Disease**

First and Second Line Systemic Treatment of Acute Graft versus Host Disease: Recommendations of the American Society of Blood and Marrow Transplantation

The guidelines recommend that the use of 6-methylprednisolone or prednisone alone is the standard of care for initial treatment of acute Graft-versus-Host Disease. From studies combining the use of other immunosuppressive agents combined with glucocorticoid therapy, survival and response data do not support this approach as standard of care. The guideline further states for second line therapy that the evaluation of six month survival estimates does not support the choice of any specific agent. The guidelines lists as second line option include (not all inclusive): etanercept, daclizumab plus etanercept, daclizumab plus infliximab, daclizumab plus etanercept plus horse antithymocyte globulin. Furthermore, results provide no evidence that any specific agent should be avoided for secondary therapy of Graft versus Host Disease. There are few prospective comparative studies that have been conducted to determine the efficacy and safety of second line therapy for Graft versus Host Disease. The guideline states that this leads clinicians to rely on reports of retrospective studies and single arm phase II studies to evaluate the benefits of treatment; and further states the comparison between these studies is complicated due to the lack of standardized endpoints and due to the small numbers of patients within the studies. (Martin, 2012)

**Diagnosis and management of acute Graft Versus Host Disease from the British Society of Hematology Guidelines and British Society of Blood and Marrow Transplant**

The management of Grade I Graft versus Host Disease should include topical therapy and optimized calcineurin inhibitors levels without the need for additional systemic immunosuppression.

For the first line treatment of Grade II through IV disease, systemic corticosteroids are recommended for first line therapy for Grade II through IV Graft versus Host Disease. For second line treatment, the following agents are suggested for use in the second line treatment of steroid-refractory acute Graft versus Host Disease: anti-tumor necrosis factor alpha antibodies, extracorporeal photopheresis, mammalian target of rapamycin inhibitors, mycophenolate mofetil, interleukin-2 receptor antibodies. Lastly, for third line treatment, the following agents are suggested in acute steroid-refractory Graft versus Host Disease as third line agent: alemtuzumab, pentostatin, mesenchymal stem cells and methotrexate. (Dignan, 2012)
Polyarticular Juvenile Idiopathic Arthritis
A randomized, controlled clinical study found favorable results for infliximab in polyarticular JIA. 122 children with persistent polyarticular JIA despite prior methotrexate therapy were randomized to receive infliximab or placebo for 14 weeks, after which all children received infliximab through week 44. Patients received methotrexate plus infliximab 3 mg/kg through week 44, or methotrexate plus placebo for 14 weeks followed by MTX plus infliximab 6 mg/kg through week 44. The investigators reported that a higher proportion of patients in the 3 mg/kg infliximab group than in the placebo group had achieved responses according to the ACR Pediatric 30 (Pedi 30) criteria for improvement at week 14 (63.8% and 49.2%, respectively), but the between-group difference in this primary efficacy end point was not statistically significant (p = 0.12). The investigators reported that, by week 16, after the crossover from placebo to infliximab 6 mg/kg when all patients were receiving infliximab, an ACR Pedi 30 response was achieved in 73.2% of all patients. By week 52, ACR Pedi 50 and ACR Pedi 70 responses had been reached in 69.6% and 51.8%, respectively, of patients. (Ruperto, 2008)

An open-label extension of this study of JIA concluded that infliximab was safe and effective in the long-term, but had a high discontinuation rate. Seventy-eight of the 122 subjects from the 2007 study entered this extension study. Infusion reactions occurred in 32% (25/78) of patients, with a higher incidence in patients positive for antibodies to infliximab (58%, 15/26). At four years, the proportions of patients achieving ACR-Pedi-30/50/70/90 response criteria and inactive disease status were 44%, 40%, 33%, 24%, and 13%, respectively. (Ruperto, 2010)

Chronic Pulmonary Sarcoidosis
Baughman et al conducted a Phase 2, multicenter, randomized, double-blind, placebo controlled trial in patients with chronic pulmonary sarcoidosis (N=138). Patients were randomized to receive intravenous infusions of infliximab (3 or 5 mg/kg) or placebo at weeks 0, 2, 6, 12, 18, and 24 and were followed through Week 52. The primary endpoint was the change from baseline to week 24 in percent of predicted forced vital capacity (FVC). Low-dose infliximab increased the percent of predicted forced vital capacity compared with baseline versus placebo (no change) at evaluations performed at weeks 24 and 52. Results of post hoc exploratory analyses did suggest those patients with more severe disease did tend to benefit more from infliximab. This trial has been critiqued for its small size and clinically insignificant effect size. (Baughman, 2006) Baughman also conducted a subset analysis for chronic cutaneous sarcoidosis. Of 138 patients, the subset analysis evaluated 17 patients with chronic facial and 9 patients with nonfacial skin involvement. An improvement was observed in 5 patients treated with placebo and 12 patients treated with infliximab from baseline to weeks 12 and 24 in desquamation and induration at week 24. (Baughman, 2016)

Rossman et al conducted a small (N=19) double-blind, placebo-controlled study with active pulmonary sarcoidosis. Patients were randomized to receive infliximab 5 mg/kg IV at weeks 0 and 2 and open-label infliximab 5 mg/kg for all subjects at weeks 6 and 14. The primary endpoint of the study was the mean relative change in vital capacity. Secondary outcome measures included chest radiographs, dyspnea score, and health-related survey. At week 6, infliximab 5 mg/kg had an increased percent change in expected vital capacity of 15.22% versus placebo at 8.39%. Rossman et al did state there was a trend toward vital capacity in the infliximab group, however, it did not meet statistical significant. At week 6, the infliximab group showed slight improvement in the following secondary outcomes: radiological findings on chest x-ray, dyspnea scores, and the health-related survey. (Rossman, 2006)

Hidradenitis Suppurativa
An evidence-based approach to the treatment of hidradenitis suppurativa/acne inversa has been published, based on the European guidelines for hidradenitis suppurativa. Adalimumab is considered at first line biologic therapy. If there is no response after 16 weeks of adalimumab treatment, other treatments should be considered. Infliximab is considered as a second line biologic treatment option. If there is a failure to respond after 12 weeks of infliximab treatment, other treatment methods must be considered. (Gulliver, 2016)

Uveitis
Results from several controlled clinical trials show that repeated infusions of infliximab, with or without concomitant methotrexate treatment, can reduce the signs and symptoms of inflammatory diseases of the eye. It is typically administered intravenously at 2 to 5 mg/kg every 4 weeks for noninfectious uveitic diseases, with the
length of treatment dictated by the clinical response. Etanercept is used less widely than infliximab due to decreased efficacy as well as the possible immunogenicity of the drug itself. (Tasman, 2009)

In 2014, the American Uveitis Society published a systemic review of the literature regarding the treatment with Anti Tumor Necrosis Factors for oculatory inflammatory disorders. The Society rated “good-quality” evidence and a strong recommendation for infliximab (Remicade) for Uveitis associated with Behcet’s disease, Ankylosing Spondylitis, inflammatory bowel disease or Psoriatic Arthritis. On the other hand, the Society stated discretionary recommendations based on what they defined as a lower quality of evidence for uveitis associated with sarcoidosis, birdshot chorioretinitis or posterior uveitis. (Levy-Clark, 2014)

**Experimental, Investigational, Unproven Uses**

Brooklyn and colleagues conducted a double-blind trial in 30 patients with pyoderma gangrenosum with or without underlying inflammatory bowel disorder. Patients were randomized to receive infliximab 5 mg/kg or placebo. The results demonstrated that significantly more patients showed improvement based on clinician and patient assessment in the infliximab group (46%) compared with the placebo group (6%). At week 6, 69% of patients who received infliximab (n = 29) showed improvement, with complete remission achieved in 21%. No improvement was seen in 31% of patients. (Brooklyn, 2006)

**Coding/ Billing Information**

*Note:* 1) This list of codes may not be all-inclusive.
2) 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:**

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**References**


