MEDICAL MUTUAL®

Drug Policy

Policy:	**200807**	**Initial Effective Date: 12/01/2008**
Code(s):	**HCPCS J1745, Q5103, Q5104, Q5109**	**Annual Review Date: 09/20/2018**
SUBJECT:	**Remicade® (infliximab)** **Inflectra (infliximab-dyyb)** **Renflexis (infliximab-abda)** **Ixifi (infliximab-qbtx)**	**Last Revised Date: 12/26/2018**

Prior approval is required for some or all procedure codes listed in this Corporate Drug Policy.

OVERVIEW

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

Inflectra and Renflexis were approved as biosimilar to Remicade, indicating no clinically meaningful differences in safety and effectiveness and the same mechanism of action, route of administration, dosage form, and strength as Remicade.[117] However, minor differences in clinically inactive components are allowed.

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

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

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

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

Disease Overview

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

Guidelines

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

Safety

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

MEDICAL MUTUAL®

Drug Policy

Policy Statement
This policy involves the use of infliximab products (Inflectra, Remicade, and Renflexis). Prior authorization is recommended for medical benefit coverage of infliximab. Coverage is recommended for those who meet the conditions of coverage in the **Criteria, Dosing, Initial/Extended Approval, Duration of Therapy, and Labs/Diagnostics** for the diagnosis provided. **Waste Management** applies for all covered conditions. **Conditions Not Recommended for Approval** are listed following the recommended authorization criteria and Waste Management section.

Because of the of the specialized skills required for evaluation and diagnosis of patients treated with Remicade,Inflectra and Renflexis as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Remicade, Inflectra and Renflexis to be prescribed by or in consultation with a physician who specializes in the condition being treated.

All approvals for initial therapy are provided for the initial approval duration noted below; if reauthorization is required, a response to therapy is required for continuation of therapy.

The Site of Care Medical Necessity Criteria applies to initial therapy and reauthorizations.

Recommended Authorization Criteria

Food and Drug Administration (FDA)-Approved Indications

1. **Rheumatoid Arthritis (RA)**.

Criteria. *The patient must meet the following criteria (a, b,c AND d):*

a) Patient meets ONE of the following conditions (i,or ii):
- **i.** Patient will be taking infliximab in combination with methotrexate (MTX)[1] or one other traditional disease-modifying antirheumatic drug (DMARD) [e.g., leflunomide, sulfasalazine, hydroxychloroquine]
- **ii.** Patient has a contraindication or intolerance to MTX and leflunomide, as determined by the prescribing physicianAND

b) Patient meets ONE of the following conditions (i, ii, or iii):[17]
- **i.** Patient has tried one DMARD (brand or generic; oral or injectable) for at least 3 months, [this includes patients who have tried other biologic DMARDs for at least 3 months]; OR
- **ii.** Patient has a contraindication or intolerance to MTX and leflunomide, as determined by the prescribing physician; OR
- **iii.** Patient has early RA (defined as disease duration of < 6 months) with at least one of the following features of poor prognosis: functional limitation (e.g., based on health assessment questionnaire disability index [HAQ-DI] score); extraarticular disease such as rheumatoid nodules, RA vasculitis, or Felty's syndrome; positive rheumatoid factor or anti-cyclic citrullinated peptide (anti-CCP) antibodies; or bony erosions by radiograph;[17] AND

c) Infliximab is prescribed by or in consultation with a rheumatologist; AND

d) Site of care medical necessity is met*.

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

Dosing in RA. *Dosing must meet one of the following (a OR b)*:[1,65]

a) The initial dose is 3 mg per kg IV infusion followed by additional similar doses at 2 and 6 weeks after the first infusion, and then every 8 weeks thereafter.

b) If the patient has an inadequate response after ≥ 2 months of therapy, the dose may be adjusted:

- **i.** The dose can be increased up to a maximum of 10 mg/kg.
- **ii.** In patients who lose response before the next dose is scheduled, the interval can be decreased to every 7, 6, 5, or 4 weeks or the dose per infusion can be increased.
- **iii.** The maximum dose is 10 mg/kg and the shortest interval is every 4 weeks.

It has been shown that increasing the dose or shortening the dosing interval of infliximab may be beneficial in patients with RA.[1,65] The criteria for an inadequate response after ≥ 2 months of therapy are recommended based on the professional opinion of specialized physicians.

Note: Data are emerging concerning tapering of infliximab dosage in patients with inflammatory conditions who are in remission or have low disease activity.[110-113] At this time, there is not a consensus regarding tapering. Therefore, alternate doses (e.g., lower dosages or extended treatment intervals) will be evaluated on a case-by-case basis. The 2015 ACR guidelines for RA mention tapering, defined as scaling back therapy (reducing dose or frequency) as a treatment option for patients who are in remission.[18] Although specific tapering schedules are not recommended, it is noted that minimizing therapy may decrease toxicity and lowers the risk of treating patients unnecessarily. 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.

Initial Approval/Extended Approval.[17]

a) *Initial Approval*. Approve for 3 months (which is 3 doses administered at Weeks 0, 2, and 6).

b) *Extended Approval*. Approve for an additional 12 months of therapy if the patient has responded (e.g., less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths; improved laboratory values; reduced dosage of corticosteroids), as determined by the prescribing physician. The patient may not have a full response, but there should have been a recent or past response to infliximab.

In clinical trials with infliximab, some patients have started to improve according to ACR 20 response within 2 weeks of starting therapy.[1] Clinically significant, important responses include patient-oriented measures such as the HAQ-DI, patient's global visual analogue scale (VAS), and Short Form (SF-36) Health Survey, or physician measures such as the joint count.[65]

Duration of Therapy in RA. Indefinite if the patient is responding.

Labs/Diagnostics. None required.

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2. Ankylosing Spondylitis (AS).

Criteria. *Patient must meet the following criteria*: Infliximab is prescribed by or in consultation with a rheumatologist AND site of care medical necessity is met*.

Infliximab is indicated for ankylosing spondylitis.[1] Guidelines for axial spondyloarthritis are available from the Assessment of SpondyloArthritis International Society (ASAS)/EULAR (2016).[116] The guidelines state that biologics (e.g., TNFis, Cosentyx) should be considered in patients with persistently high disease activity despite traditional conventional treatments (e.g., nonpharmacological management, NSAIDs). For patients with primarily peripheral manifestations of axial spondylitis, local steroid injections and sulfasalazine may be considered as conventional treatment; however, these are not considered for patients who present primarily with axial disease. Furthermore, the guidelines state that patients with purely axial disease should not be treated with conventional synthetic DMARDs. Guidelines from the American College of Rheumatology (ACR) and the Spondyloarthritis Research and Treatment Network (SPARTAN) [2015] make recommendations for treatment of AS.[19] TNF inhibitors (e.g., Cimzia, Enbrel, Humira, infliximab, Simponi SC) are recommended for patients who have active disease despite treatment with an NSAID. There is not a preference for TNF inhibitor, except for in the cases of concomitant inflammatory bowel disease or recurrent iritis, when a monoclonal antibody (Humira, infliximab) is recommended over Enbrel. According to Assessments in Ankylosing Spondylitis/European League Against Rheumatism (ASAS/EULAR) 2010 recommendations for ankylosing spondylitis, all patients should have an adequate trial of at least two nonsteroidal anti-inflammatory drugs (NSAIDs) for pain and stiffness, unless contraindicated.[20-22] Recommendations for other therapies before receiving a TNF blocker vary according to the manifestations of the disease, level of current symptoms, clinical findings, etc. According to these recommendations, patients with pure axial manifestations do not have to try traditional DMARDs before anti-TNF agents such as Infliximab; patients with symptomatic peripheral arthritis should have an insufficient response to at least one local corticosteroid injection, if appropriate; patients with peripheral arthritis should normally have a trial of a DMARD, preferably sulfasalazine; and patients with enthesitis should try appropriate local therapy (e.g., corticosteroid injection in selected cases). In patients with AS, concomitant treatment with a nonbiologic DMARD does not add to the safety or efficacy with an anti-TNF inhibitor.[23]

Dosing in AS. *Dosing must meet ONE of the following (a OR b)*:[1,102]

a) The initial dose is 5 mg per kg IV infusion followed by additional similar doses at 2 and 6 weeks after the first infusion, and then every 6 weeks thereafter.

b) If the patient has an inadequate response after ≥ 2 months of therapy, the dose may be adjusted:

- **i.** The dose can be increased up to a maximum of 10 mg/kg.
- **ii.** In patients who lose response before the next dose is scheduled, the interval can be decreased to every 5 or 4 weeks or the dose per infusion can be increased.
- **iii.** The maximum dose is 10 mg/kg and the shortest interval is every 4 weeks.

In certain cases, changes in infliximab dosage or dosing interval are recommended for patients with AS who initially respond and then lose that response.[102] The criteria for dosing ranges and an inadequate response after ≥ 2 months of therapy are recommended based on the professional opinion of specialized physicians.

Note: Data are emerging concerning tapering of infliximab dosage in patients with inflammatory conditions who are in remission or have low disease activity.[110-113] At this time, there is not a consensus regarding tapering. Therefore, alternate doses (e.g., lower dosages or extended treatment intervals) will be evaluated on a case-by-case basis.

Initial Approval/Extended Approval.[102]

a) *Initial Approval*. Initial approval is for 3 months of therapy (3 doses given as Weeks 0, 2, and 6).

b) *Extended Approval*. Approve for an additional 12 months of therapy if the patient has responded (e.g., less joint pain, morning stiffness, or fatigue; improved mobility [e.g., improved spinal mobility]; decreased soft tissue swelling in joints or tendon sheaths; improvements in acute phase reactants [e.g., erythrocyte sedimentation rate {ESR}, C-reactive protein {CRP}]) as determined by the prescribing physician. The patient may not have a full response, but there should have been a recent or past response to infliximab.

Duration of Therapy in AS. Indefinite if the patient is responding.

Labs/Diagnostics. None required.

~~3.~~ Crohn's Disease in a Patient ≥ 6 Years of Age.

Criteria. *The patient must meet the following criteria (a, b, AND c)*:

a) The patient meets ONE of the following conditions (i, ii, iii, or iv):

- **i.** The patient has tried or is currently taking corticosteroids, or corticosteroids are contraindicated in this patient (Note: Examples of corticosteroids are prednisone, methylprednisolone);[27] OR
- **ii.** The patient has tried one other agent for Crohn's disease (e.g., azathioprine, 6-mercaptopurine, MTX, Cimzia, Humira, or Entyvio);[1] OR
- **iii.** The patient has enterocutaneous (perianal or abdominal) or rectovaginal fistulas;[1] OR
- **iv.** The patient has had ileocolonic resection (to reduce the chance of Crohn's disease recurrence);[23-26] AND

b) Infliximab is prescribed by or in consultation with a gastroenterologist; AND

c) Site of care medical necessity is met*.

Infliximab is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult and pediatric patients ≥ 6 years of age with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy.[1] Infliximab is also indicated for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing Crohn's disease. Infliximab has also been shown to reduce the chance of recurrence of symptoms after surgery in patients with Crohn's disease.[24-27] In one study, patients treated with Infliximab following illeocolonic resection of Crohn's disease noticed a significant decrease in Crohn's Disease Activity Index (CDAI) score at Month 2 ($P < 0.01$ compared with baseline); this decrease in CDAI was not found in study patients treated post-resection with mesalamine or azathioprine.[25] The American Gastroenterological Association (AGA) has guidelines for Crohn's disease (2013).[28] For induction therapy,

TNF blockers are listed as a strong recommendation for patients with moderately severe CD (moderate-quality evidence). In the professional opinion of specialist physicians reviewing the data, we have adopted these criteria.

Dosing in Crohn's Disease. *Dosing must meet one of the following (a OR b)*:[1,102]

a) The initial dose is 5 mg per kg IV infusion followed by additional similar doses at 2 and 6 weeks after the first infusion, and then every 8 weeks thereafter.

b) If the patient has an inadequate response to the initial dosage, the dose may be adjusted:

- **i.** The dose can be increased up to a maximum of 10 mg/kg.
- **ii.** In patients who lose response before the next dose is scheduled, the interval can be decreased to every 7, 6, 5, or 4 weeks or the dose per infusion can be increased.
- **iii.** The maximum dose is 10 mg/kg and the shortest interval is every 4 weeks.

Note: Data are emerging concerning tapering of infliximab dosage in patients with inflammatory conditions who are in remission or have low disease activity.[110-113] At this time, there is not a consensus regarding tapering. Therefore, alternate doses (e.g., lower dosages or extended treatment intervals) will be evaluated on a case-by-case basis.

Initial Approval/Extended Approval.[102]

a) *Initial Approval*. Initial approval is for 3 months (3 doses given at Weeks 0, 2 and 6).

b) *Extended Approval*. Approve for an additional 12 months of therapy if the patient received 3 doses of infliximab and had had a response to therapy, as determined by the prescribing physician. The patient may not have a full response by Month 2 or 3, but there should be some response.

Duration of Therapy in Crohn's Disease. Indefinite if the patient is responding.

Labs/Diagnostics. None required.

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4. Plaque Psoriasis.

Criteria. *Patient must meet the following criteria (a, b, cAND d):*

a) The patient is an adult greater than or equal to 18 years of age; AND

b) The patient meets ONE of the following conditions (i, ii, or iii):

- **i.** The patient has tried at least ONE of the following therapies for at least 3 months for plaque psoriasis: an oral therapy for psoriasis (e.g., MTX, cyclosporine, Soriatane® [acitretin]); oral methoxsalen plus ultraviolet A light (PUVA); or a biologic agent (e.g., Enbrel, Humira, or Stelara™ [ustekinumab]); OR
- **ii.** The patient experienced an intolerance to a trial of at least one oral or biologic therapy for plaque psoriasis (e.g., MTX, cyclosporine, Soriatane, Enbrel, Humira, or Stelara); OR
- **iii.** The patient has a contraindication to one oral agent for psoriasis such as MTX, as determined by the prescribing physician.

c) Infliximab is prescribed by or in consultation with a dermatologist; AND

d) Site of care medical necessity is met*

Infliximab is indicated for plaque psoriasis.[1] Guidelines for treatment of plaque psoriasis recommend topical therapy for limited disease.[29-30] However, for patients with chronic plaque psoriasis that does not respond to topical therapies or patients with more extensive disease, systemic therapy may be used. The traditional systemic agents for plaque psoriasis are MTX, acitretin, and cyclosporine. A biologic agent such as infliximab is an option for patients who are candidates for phototherapy or systemic therapy, especially those who are intolerant of or unresponsive to traditional systemic agents. In the professional opinion of specialist physicians reviewing the data, we have adopted the criteria requirements for previous therapy.

Dosing in Plaque Psoriasis. *Dosing must meet ONE of the following (a OR b):*[1,102]

a) The initial dose is 5 mg per kg IV infusion followed by additional similar doses at 2 and 6 weeks after the first infusion, and then every 8 weeks thereafter.

b) If the patient has an inadequate response to ≥ 2 months of therapy, the dose may be adjusted:

- **i.** The dose can be increased up to a maximum of 10 mg/kg.
- **ii.** In patients who lose response before the next dose is scheduled, the interval can be decreased to every 7, 6, 5, or 4 weeks or the dose per infusion can be increased.
- **iii.** The maximum dose is 10 mg/kg and the shortest interval is every 4 weeks.

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.[102] The criteria for an inadequate response after ≥ 2 months of therapy are recommended based on the professional opinion of specialized physicians.

Initial Approval/Extended Approval.[102]

a) *Initial Approval*. Initial approval is for 3 months of therapy (3 doses given at Weeks 0, 2 and 6).

b) *Extended Approval*. Approve for an additional 12 months of therapy if the patient has responded (for example, there is less induration, erythema, scaling, itching) as determined by the prescribing physician. The patient may not have a full response by Month 2 or 3, but there should be some response.

In clinical trials, patients were significantly improved by Week 10 of therapy.[1]

Duration of Therapy in Plaque Psoriasis. Indefinite if the patient is responding.

Labs/Diagnostics. None required.

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5. Psoriatic Arthritis (PsA).

a) **Criteria.** *The patient must meet the following criteria:* Infliximab is prescribed by or in consultation with a rheumatologist or a dermatologist AND site of care medical necessity is met*.

Infliximab is indicated for PsA.[1] In clinical trials, infliximab was effective in patients with active PsA despite therapy with a DMARD or NSAID. There are few well-controlled, prospective studies with adequate duration that have

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

Dosing in PsA. *Dosing must meet ONE of the following (a OR b)*:[1,102]

a) The initial dose is 5 mg per kg IV infusion followed by additional similar doses 2 and 6 weeks after the first infusion, and then every 8 weeks thereafter.

b) If the patient has an inadequate response to ≥ 2 months of therapy, the dose may be adjusted:
- **i.** The dose can be increased up to a maximum of 10 mg/kg.
- **ii.** In patients who lose response before the next dose is scheduled, the interval can be decreased to every 7, 6, 5, or 4 weeks and/or the dose per infusion can be increased.
- **iii.** The maximum dose is 10 mg/kg and the shortest interval is every 4 weeks.

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.[102] The criteria for an inadequate response after ≥ 2 months of therapy are recommended based on the professional opinion of specialized physicians.

Note: Data are emerging concerning tapering of infliximab dosage in patients with inflammatory conditions who are in remission or have low disease activity.[110-113] At this time, there is not a consensus regarding tapering. Therefore, alternate doses (e.g., lower dosages or extended treatment intervals) will be evaluated on a case-by-case basis.

Initial Approval/Extended Approval.[102]

a) *Initial Approval*. Initial approval is for 3 months of therapy (three doses at Weeks 0, 2, and 6).

b) *Extended Approval*. Approve for an additional 12 months of therapy if the patient has responded (e.g., less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths; improvements in acute phase reactants [e.g., CRP]) as determined by the prescribing physician. The patient may not have a full response by Month 2 or 3, but there should be some response.

Duration of Therapy in PsA. Indefinite if the patient is responding.

Labs/Diagnostics. None required.

6. Ulcerative Colitis (UC) in a Patient ≥ 6 Years of Age.

Criteria. *Patient must meet the following criteria (a, b, AND c):*

a) The patient meets one of the following conditions (i or ii):
- **i.** Patient has had a 2-month trial of one systemic corticosteroid (e.g., prednisone, methylprednisolone) or 6-mercaptopurine, azathioprine, cyclosporine, or tacrolimus or was intolerant to one of these agents for ulcerative colitis;[1] NOTE: A previous trial of a biologic (e.g., an adalimumab product [e.g., Humira], Simponi SC [golimumab SC injection], or Entyvio [vedolizumab IV infusion] also counts as a trial of one systemic agent for UC); OR
- **ii.** The patient has pouchitis AND has tried therapy with an antibiotic (e.g., metronidazole, ciprofloxacin), probiotic, corticosteroid enema, or Rowasa® (mesalamine) enema;[32-34,97] AND

b) Infliximab is prescribed by or in consultation with a gastroenterologist; AND

c) Site of care medical necessity is met*.

Infliximab is indicated for adults and pediatric patients ≥ 6 years of age with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.[1,33] Remicade is also approved in pediatric patients ≥ 6 years of age with ulcerative colitis; although Inflectra does not share this indication, the prescribing information notes that pediatric assessment demonstrated safety and efficacy of Inflectra in this indication.[117] Infliximab has been effective in cases of refractory pouchitis.[34] Clinical guidelines for the management of pouchitis, published in 2009, and ulcerative colitis practice guidelines from the American College of Gastroenterology (ACG) [2010] indicate that first-line therapy for pouchitis is antibiotic therapy (e.g. metronidazole, ciprofloxacin).[35-36] Other treatment options include maintenance probiotics, oral or topical budesonide, anti-inflammatory drugs (e.g. mesalamine), or immunosuppressive drugs (e.g. Infliximab).

Dosing in Ulcerative Colitis. *Dosing must meet ONE of the following (a OR b)*:[1,97]

a) The initial dose is 5 mg per kg IV infusion followed by additional similar doses 2 and 6 weeks after the first infusion, and then every 8 weeks thereafter.

b) If the patient has an inadequate response to the initial dosage, the dose may be adjusted:
- **i.** The dose can be increased up to a maximum of 10 mg/kg.
- **ii.** In patients who lose response before the next dose is scheduled, the interval can be decreased to every 7, 6, 5, or 4 weeks or the dose per infusion can be increased.
- **iii.** The maximum dose is 10 mg/kg and the shortest interval is every 4 weeks.

Initial Approval/Extended Approval.[102]

a) *Initial Approval*. Approve for 3 months (three doses given at Weeks 0, 2, and 6).

b) *Extended Approval*. Approve for an additional 12 months of therapy if the patient has responded as determined by the prescribing physician. The patient may not have a full response by Month 2 or 3 (after three doses), but there should be some response.

Duration of Therapy in Ulcerative Colitis. Indefinite if the patient is responding.

Labs/Diagnostics. None required.

Other Uses with Supportive Evidence

1. **Behcet's Disease.**

Criteria. *Patient must meet the following criteria (a, b, AND c):*

a) The patient meets ONE of the following conditions (i or ii):
   - **i.** The patient has tried at least ONE conventional therapy (e.g., systemic corticosteroids, immunosuppressants [azathioprine, MTX, mycophenolate mofetil, cyclosporine, tacrolimus, Leukeran® [chlorambucil], cyclophosphamide], interferon alfa) or Humira or Enbrel; OR
   - **ii.** The patient has ophthalmic manifestations of Behcet's disease; AND

b) Infliximab is prescribed by or in consultation with a rheumatologist, dermatologist, ophthalmologist, gastroenterologist, or neurologist; AND

c) Site of care medical necessity is met*.

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

Dosing in Behcet's Disease. *Dosing must meet ONE of the following (a OR b):*[35, 104]

a) The initial dose is 3 to 5 mg per kg IV infusion followed by additional similar doses at 2 and 6 weeks after the first infusion, then every 6 to 8 weeks thereafter.

b) If the patient has an inadequate response after ≥ 2 months of therapy, the dose may be adjusted (i, ii, or iii):
   - **i.** The dose can be increased up to a maximum of 10 mg/kg with the same treatment interval (every 6 to 8 weeks); OR
   - **ii.** The dose may remain the same (3 to 5 mg/kg) and the interval can be decreased to every 7, 6, 5, or 4 weeks; OR
   - **iii.** In selected case, patients may be titrated to the maximum dose (10 mg/kg) and the shortest dosing interval (every 4 weeks).

Patients with Behcet's disease have been treated with a range of doses (3 to 10 mg/kg).[35] The most common treatment interval documented in the literature has been every 6 to 8 weeks. However, patients with Behcet's disease may present with uveitis[35] where more frequent administration (such as every 4 weeks) is used.[52-53] In the professional opinion of specialist physicians reviewing the data, we have adopted these dosing ranges.

Note: Data are emerging concerning tapering of infliximab dosage in patients with inflammatory conditions who are in remission or have low disease activity.[110-113] At this time, there is not a consensus regarding

tapering. Therefore, alternate doses (e.g., lower dosages or extended treatment intervals) will be evaluated on a case-by-case basis.

Initial Approval/Extended Approval.[35]
a) *Initial Approval*. Approve for 3 months (which is three doses administered at Weeks 0, 2, and 6).
b) *Extended Approval*. Approve for an additional 12 months of therapy if the patient has responded, as determined by the prescribing physician. The patient may not have a full response by Month 2 or 3, but there should be some response.

Duration of Therapy in Behcet's Disease. Indefinite if the patient is responding.

Labs/Diagnostics. None required.

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2. Indeterminate Colitis in a Patient ≥ 6 Years of Age (defined as colitis that cannot be classified with certainty as either ulcerative colitis or Crohn's disease).

Criteria. *Patient must meet ALL of following criteria (a, b, c ,d, AND e)*:[37]
a) Patient has tried one systemic corticosteroid; AND
b) Patient has tried mesalamine; AND
c) Patient has tried either azathioprine or 6-mercaptopurine; AND
d) Infliximab is prescribed by or in consultation with a gastroenterologist; AND
e) Site of care medical necessity is met*.

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

Dosing in Indeterminate Colitis in a Patient ≥ 6 years of age. *Dosing must meet ONE of the following (a OR b)*:[37]
a) The initial dose is 5 mg per kg IV infusion followed by additional similar doses at 2 and 6 weeks after the first infusion, and then every 8 weeks thereafter.
b) If the patient has an inadequate response to the initial dosage, the dose may be adjusted:
  i. The dose can be increased up to a maximum of 10 mg/kg.
  ii. The interval can be decreased to every 7, 6, 5, or 4 weeks or the dose per infusion can be increased.
  iii. The maximum dose is 10 mg/kg and the shortest interval is every 4 weeks.

Initial Approval/Extended Approval.
a) *Initial Approval*. Approve for 4 months of therapy (four doses administered at Weeks 0, 2, 6, and 14).
b) *Extended Approval*. Approve for an additional 12 months of therapy if the patient has responded as determined by the prescribing physician. The patient may not have a full response by Month 4 or 5 (after four doses), but there should be some response.

Duration of Therapy in Indeterminate Colitis. Indefinite if the patient is responding.

Labs/Diagnostics. None required.

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3. Juvenile Idiopathic Arthritis (JIA) or Juvenile Rheumatoid Arthritis (JRA) (regardless of type of onset) [Note: This includes patients with juvenile spondyloarthropathy/active sacroiliac arthritis].

Criteria. *The patient must meet the following criteria (a, b,c AND d):*

b) Patient meets ONE of the following conditions (i,or ii):

i. Patient will be taking infliximab in combination with methotrexate (MTX)[1] or one other traditional disease-modifying antirheumatic drug (DMARD) [e.g., leflunomide, sulfasalazine, hydroxychloroquine]

ii. Patient has a contraindication or intolerance to MTX and leflunomide, as determined by the prescribing physicianAND

c) Patient meets ONE of the following conditions (i, or ii):[17]

i. Patient has tried one other agent for this condition (e.g., MTX, sulfasalazine, or leflunomide, an NSAID, or one biologic DMARD [e.g., Humira, Orencia® {abatacept for IV infusion}, Enbrel, Kineret® {anakinra for SC injection}, Actemra® {tocilizumab for IV infusion}]);[39] OR

ii. Patient has aggressive disease, as determined by the prescribing physician;[39] AND

d) Infliximab is prescribed by or in consultation with a rheumatologist; AND

e) Site of care medical necessity is met*.

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

Dosing in JIA/JRA. *Dosing must meet one of the following (a OR b):*[44]

a) The initial dose is 3 to 6 mg per kg IV infusion followed by additional similar doses at 2 and 6 weeks after the first infusion, and then every 8 weeks thereafter.

b) If the patient has an inadequate response after ≥ 2 months of therapy, the dose may be adjusted to a maximum of 10 mg/kg maintenance dosing (every 8 weeks).

Most of the literature evaluating infliximab in JIA has evaluated 3 to 6 mg/kg dosing.[1,39-44] The criteria for dosing ranges and an inadequate response after ≥ 2 months of therapy are recommended based on the professional opinion of specialized physicians.

Note: Data are emerging concerning tapering of infliximab dosage in patients with inflammatory conditions who are in remission or have low disease activity.[110-113] At this time, there is not a consensus regarding tapering. Therefore, alternate doses (e.g., lower dosages or extended treatment intervals) will be evaluated on a case-by-case basis.

Initial Approval/Extended Approval.

a) *Initial Approval*. Approve for 3 months (three doses, usually given at Weeks 0, 2, and 6).

b) *Extended Approval*. Approve for an additional 12 months of therapy if the patient has responded (e.g., has improvement in limitation of motion; less joint pain or tenderness; decreased duration of morning stiffness or fatigue; improved function or activities of daily living; reduced dosage of corticosteroids), as determined by the prescribing physician. The patient may not have a full response by Month 2 to 3, but there should be some response.

Duration of Therapy in JIA/JRA. Indefinite in patients who are responding.

Labs/Diagnostics. None required.

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4. Still's Disease.

Criteria. *Patient must meet ALL of the following criteria (a, b, c, AND d)*:

a) Patient has tried one corticosteroid;[48] AND

b) Patient has tried one conventional synthetic DMARD such as methotrexate given for at least 2 months or was intolerant to a conventional synthetic DMARD;[48] AND

c) Infliximab is prescribed by or in consultation with a rheumatologist; AND

d) Site of care medical necessity is met*.

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

Dosing in Still's Disease. *Dosing must meet the following:* The initial dose is 3 to 6 mg per kg IV infusion followed by additional similar doses at 2 and 6 weeks after the first infusion, and then every 8 weeks thereafter.

Much of the literature involving Still's disease has evaluated the 3 mg/kg dose of infliximab.[86] However, Still's disease is now considered a similar entity to systemic JIA (SJIA) where other doses of infliximab have been evaluated.[84] In the professional opinion of specialist physicians reviewing the data, we have adopted these dosing ranges.

Note: Data are emerging concerning tapering of infliximab dosage in patients with inflammatory conditions who are in remission or have low disease activity.[110-113] At this time, there is not a consensus regarding tapering. Therefore, alternate doses (e.g., lower dosages or extended treatment intervals) will be evaluated on a case-by-case basis.

Initial Approval/Extended Approval.[99]

a) *Initial Approval*. Approve for 3 months (doses at Weeks 0, 2, and 6).

b) *Extended Approval*. Approve for an additional 12 months of therapy if the patient has responded, as determined by the prescribing physician. The patient may not have a full response by Month 2 or 3, but there should be some response.

Duration of Therapy in Still's Disease. Indefinite if the patient is responding.

Labs/Diagnostics. None required.

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5. Spondyloarthritis (SpA), Subtypes Other than Ankylosing Spondylitis or Psoriatic Arthritits (e.g., undifferentiated arthritis, non-radiographic axial SpA, Reactive Arthritis [Reiter's disease]) [NOTE: For AS or PsA, refer to the respective criteria under FDA-approved indications].

Criteria. *Patient must meet BOTH of the following criteria (A, B AND C):*

A) The patient meets one of the following conditions (i or ii):

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

B) Infliximab is prescribed by or in consultation with a rheumatologist; AND

C) Site of care medical necessity is met*.

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

should have a trial of at least two NSAIDS over a 4-week period at the maximum recommended or tolerated dose. Patients who have predominantly axial manifestations are not recommended for a conventional synthetic DMARD trial prior to beginning therapy with a TNF blocker. In patients with symptomatic peripheral arthritis, a therapeutic trial of a conventional synthetic DMARD is recommended (preferably sulfasalazine).

Dosing in SpA. *Dosing must meet ONE of the following:*

~~a.~~ The initial dose is 5 mg per kg IV infusion followed by additional similar doses at 2 and 6 weeks after the first infusion, and then every 6 to 8 weeks thereafter.

b. If the patient has an inadequate response after ≥ 2 months of therapy, the dose may be adjusted:

i. The dose can be increased up to a maximum of 10 mg/kg.

ii. In patients who lose response before the next dose is scheduled, the interval can be decreased to every 5 or 4 weeks or the dose per infusion can be increased.

iii. The maximum dose is 10 mg/kg and the shortest interval is every 4 weeks.

Note: Data are emerging concerning tapering of infliximab dosage in patients with inflammatory conditions who are in remission or have low disease activity.[110-113] At this time, there is not a consensus regarding tapering. Therefore, alternate doses (e.g., lower dosages or extended treatment intervals) will be evaluated on a case-by-case basis.

Initial Approval/Extended Approval.[50]

a) *Initial Approval*. Approve for 3 months (doses at Weeks 0, 2, and 6).

b) *Extended Approval*. Approve for an additional 12 months of therapy if the patient has responded, as determined by the prescribing physician. The patient may not have a full response by Month 2 or 3, but there should be some response.

Duration of Therapy in SpA. Indefinite if the patient is responding.

Labs/Diagnostics. None required.

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6. Uveitis.

Criteria. *Patient must meet the following criteria (a, ,b AND c):*

a. The patient has tried one of the following therapies: periocular, intraocular, or systemic corticosteroids; immunosuppressives (e.g., MTX, mycophenolate mofetil, cyclosporine, azathioprine, cyclophosphamide); or Enbrel or Humira for this condition;[52-59, 103] AND

b. Infliximab is prescribed by or in consultation with an ophthalmologist; AND

c. Site of care medical necessity is met*.

In patients with uveitis, TNF levels are increased in the serum and aqueous humor.[91] Infliximab has been effective in producing regression of symptoms and improving visual acuity in patients with panuveitis, posterior or anterior uveitis, scleritis, and retinal vasculitis; many of these patients have an underlying extraocular systemic diagnosis such as RA, ankylosing spondylitis, psoriasis, spondyloarthropathy, JIA, Behcet's disease, or Crohn's disease who were

refractory to corticosteroids and immunosuppressive agents.[91-92] Recommendations for the use of TNF blockers in ocular inflammatory disorders from the AAO (2014) note that Infliximab may be used in patients with uveitis due to various causes (e.g., spondyloarthropathy-associated or human leukocyte antigen [HLA]-B27-associated uveitis, JIA-associated uveitis, and other posterior uveitides and panuveitis syndromes).[40] Infliximab should be considered second-line in vision-threatening JIA-associated uveitis when MTX has failed or is not tolerated (strong recommendation) and vision-threatening chronic uveitis from seronegative spondyloarthropathy (strong recommendation). Infliximab may also be considered in other patients who have vision-threatening or corticosteroid-dependent disease who have failed first-line therapies. The recommendations point out that studies evaluating Infliximab in uveitis included patients with birdshot chorioretinitis (BSCR), a bilateral posterior uveitis generally treated with systemic immunomodulation; these patients showed a good response to Infliximab.

Dosing in Uveitis. *Dosing must meet ONE of the following (a OR b)*: [52-53]

a) The initial dose is 5 to 10 mg per kg IV infusion followed by additional similar doses at 2 and 6 weeks after the first infusion, then every 4 to 8 weeks thereafter.

b) If the patient has an inadequate response to the initial dosage, the dose may be adjusted. The maximum dose is 10 mg/kg and the shortest dosing interval is one dose every 4 weeks.

Initial Approval/Extended Approval.[72]

a) *Initial Approval*. Approve for 3 months (three doses administered at Weeks 0, 2, and 6).

b) *Extended Approval*. Approve for an additional 12 months of therapy if the patient has responded (e.g., decreased inflammation, reduced use of steroids or immunomodulators, and improvement in visual acuity), as determined by the prescribing physician. The patient may not have a full response by Month 2 or 3, but there should be some response.

Duration of Therapy in Uveitis. Indefinite if the patient is responding.

Labs/Diagnostics. None required.

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7. Sarcoidosis.

Criteria. Patient must meet the following criteria (A, B, C and D):

A) Patient has tried at least one corticosteroid (e.g., prednisone); AND

B) Patient has tried at least one immunosuppressive agent (e.g., methotrexate [MTX], azathioprine, cyclosporine, Leukeran) or thalidomide or chloroquine; AND

C) Infliximab is prescribed by or in consultation with a pulmonologist, ophthalmologist, or dermatologist; AND

D) Site of care medical necessity is met*.

Well-controlled studies are not available for any therapies.[67] Steroids are the standard therapy, but long-term use is limited by adverse events. Immunosuppressants have shown modest efficacy with the best results available for MTX. High levels of TNF in bronchoalveolar lavage of patients with sarcoidosis have been reported with a decrease in TNF

levels following treatment. Infliximab has been effective in controlling various manifestations of sarcoidosis in selected patients who were refractory to standard therapy.[60,68-74] In a Phase II, multicenter, double-blind trial, 138 patients with corticosteroid-dependent chronic pulmonary sarcoidosis were randomized to Infliximab 3 or 5 mg/kg or to placebo at Weeks 0, 2, 6, 12, 18, and 24 and were followed through Week 54.[75] The mean change from baseline to Week 24 in percent of predicted forced vital capacity (FVC) was an increase of 2.5% with infliximab (both groups combined) vs. no change with placebo (P = 0.038). There were no significant differences between treatment groups for any of the major secondary endpoints at Week 24.[75-76] The clinical relevance of the FVC improvement is unclear. In a post hoc analysis, patients with more severe disease tended to benefit more from infliximab.[75]

Dosing in Sarcoidosis.[67]

a) The dose is 3 to 5 mg per kg IV infusion followed by additional similar doses at 2 and 6 weeks after the first infusion, then every 6 to 8 weeks thereafter.[1]

b) In patients who lose response before the next dose (3 to 5 mg/kg) is scheduled, the interval can be decreased; the shortest dosing interval is every 4 weeks.

Note: Data are emerging concerning tapering of infliximab dosage in patients with inflammatory conditions who are in remission or have low disease activity.[110-113] At this time, there is not a consensus regarding tapering. Therefore, alternate doses (e.g., lower dosages or extended treatment intervals) will be evaluated on a case-by-case basis.

Initial approval/Extended approval.

A) Approve for 3 months (which is 3 doses administered at Weeks 0, 2, and 6).[73]

B) Approve for an additional 12 months of therapy if the patient has responded, as determined by the prescribing physician. The patient may not have a full response by Month 3, but there should be some response.

Duration of therapy in Sarcoidosis: Indefinite if the patient is responding.

Labs/Diagnostics: None required.

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8. Pyoderma Gangrenosum.

Criteria. *Patient must meet BOTH of the following criteria (A, B and C):*

A) The patient meets ONE of the following conditions (i or ii):

- **i.** The patient has tried one systemic corticosteroid (e.g., prednisone); OR
- **ii.** The patient has tried one other immunosuppressant (e.g., mycophenolate mofetil, cyclosporine) for at least 2 months or was intolerant to one of these agents; AND

B) Infliximab is prescribed by or in consultation with a dermatologist; AND

C) Site of care medical necessity is met*.

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

Dosing in Pyoderma Gangrenosum. *Dosing must meet ONE of the following (A OR B):*

A) The initial dose is 5 mg per kg IV infusion followed by additional similar doses 2 and 6 weeks after the first infusion, and then every 8 weeks thereafter.[86]

B) If the patient has an inadequate response to the initial dosage, the dose may be adjusted:

- **i.** The dose can be increased up to a maximum of 10 mg/kg.
- **ii.** The interval can be decreased to every 7, 6, 5, or 4 weeks or the dose per infusion can be increased.
- **iii.** The maximum dose is 10 mg/kg and the shortest interval is every 4 weeks.

Most literature evaluating infliximab for treatment of pyoderma gangrenosum used doses of 5 mg/kg for induction then every 8 weeks.[62] However, pyoderma gangrenosum is associated with systemic autoimmune disorders (e.g., RA, Crohn's disease, ulcerative colitis) where other doses and dosing intervals of infliximab have also been evaluated. In the professional opinion of specialist physicians reviewing the data, we have adopted this dosing for pyoderma gangrenosum.

Note: Data are emerging concerning tapering of infliximab dosage in patients with inflammatory conditions who are in remission or have low disease activity.[110-113] At this time, there is not a consensus regarding tapering. Therefore, alternate doses (e.g., lower dosages or extended treatment intervals) will be evaluated on a case-by-case basis.

Initial Approval/Extended Approval.

A) *Initial Approval*. Approve for 4 months (four doses administered at Weeks 0, 2, 6, and 14).

B) *Extended Approval*. Approve for an additional 12 months of therapy if the patient has responded, as determined by the prescribing physician. The patient may not have a full response by Month 4 or 5 (after 4 doses), but there should be some response.

Duration of therapy in Pyoderma Gangrenosum. Indefinite if the patient is responding.

Labs/Diagnostics. None required.

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9. Immunotherapy-Related Toxicities Associated with Checkpoint Inhibitor Therapy.

Criteria. *The patient must meet the ONE of following (A OR B):*

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

- **i.** The patient developed an immunotherapy-related toxicity involving the gastrointestinal system (e.g., colitis), inflammatory arthritis, or ocular toxicity (e.g., uveitis/iritis, episcleritis, blepharitis); AND
- **ii.** The patient developed this immune-related toxicity while receiving a checkpoint inhibitor (e.g., Keytruda [pembrolizumab IV infusion], Opdivo [nivolumab IV infusion], Yervoy [ipilimumab IV infusion], Tecentriq [atezolizumab IV infusion], Bavancio [avelumab IV infusion], or Imfinzi [durvalumab IV infusion]); AND
- **iii.** The patient has tried a systemic corticosteroid (e.g., methyprednisone, prednisone); AND
- **iv.** Infliximab is being prescribed by or in consultation with an oncologist, gastroenterologist, rheumatologist, or ophthalmologist.

B) Site of care medical necessity is met*.

Dosing in Immunotherapy-Related Toxicities Associated with Checkpoint Inhibitor Therapy. *Dosing must meet the following (A OR B):*

A) Initial dose is a 5 to 10 mg per kg IV infusion followed by additional similar doses at 2 and 6 weeks after the first infusion, then every 4 to 8 weeks thereafter.

B) If the patient has an inadequate response to the initial dosage, the dose may be adjusted. The maximum dose is 10 mg/kg and the shortest dosing interval is one dose every 4 weeks.

The data involving immunotherapy-related toxicities with checkpoint inhibitors are evolving. NCCN has guidelines in partnership with the American Society of Clinical Oncology (ASCO) [version 1.2018 – February 14, 2018] for Management of Immunotherapy-Related Toxicities (Immune Checkpoint Inhibitor-Related Toxicities) which include use of infliximab to manage many toxicities. Some severe toxicities (e.g., pneumonitis, cardiac toxicity, renal failure) may also be treated with infliximab but are more likely to be administered in the hospital setting; any requests for these toxicities will be evaluated on a case-by-case basis.

Initial Approval/Extended Approval:
Initial Approval: 3 months
Extended Approval: 12 months, Approve if the patient has responded and needs continued treatment, as determined by the prescribing physician.

The optimal dose and duration of therapy with infliximab is not fully understood and may vary on a case-by-case basis. In some cases only one or two doses may be needed; however, some patients may need continued treatment.

Duration of therapy in Dosing for Immunotherapy-Related Toxicities Associated with Checkpoint Inhibitor Therapy: Duration of therapy dependent upon response and resolution of symptoms, as determined by the prescribing physician.

Labs/Diagnostics: None required. However, CRP and ESR may be monitored to assess response to therapy in RA.

Waste Management for All. There is no overfill in the Remicade, Renflexis or Inflectra vials. Weight-based dosing is used; the dose should be calculated and the number of vials needed assessed.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

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

1. **Concurrent Use with a Biologic DMARD or Targeted Synthetic DMARD.** Infliximab should not be administered in combination with another biologic agent for an inflammatory condition (e.g., another TNF antagonists [e.g., Cimzia, Enbrel, Humira, or Simponi], Actemra, Kineret, Orencia, Rituxan, or Stelara). Combination therapy with two biologic agents is not recommended due to a higher rate of adverse effects with combinations and lack of additive efficacy.[93] The targeted synthetic DMARDs Xeljanz and Otezla should not be used in combination with biologic DMARDs such as infliximab.[115] Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., MTX, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with infliximab.

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

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

immunosuppressants (e.g., azathioprine, MTX, MMF, cyclophosphamide).[98-102] Infliximab has been effective in a very limited number of patients with vasculitis (e.g., RA, cryoglobulinemia, polyangiitis, polymyalgia rheumatica, Takayasu's arteritis) who were refractory to standard therapy.[98-99,103-107] However, in a randomized study in 51 patients with newly diagnosed polymyalgia rheumatica, adding Infliximab 3 mg/kg to prednisone was of no benefit and may have been harmful.[108-109]

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

Documentation Requirements:

The Company reserves the right to request additional documentation as part of its coverage determination process. The Company may deny reimbursement when it has determined that the drug provided or services performed were not medically necessary, investigational or experimental, not within the scope of benefits afforded to the member and/or a pattern of billing or other practice has been found to be either inappropriate or excessive. Additional documentation supporting medical necessity for the services provided must be made available upon request to the Company. Documentation requested may include patient records, test results and/or credentials of the provider ordering or performing a service. The Company also reserves the right to modify, revise, change, apply and interpret this policy at its sole discretion, and the exercise of this discretion shall be final and binding.

REFERENCES

1. Remicade® injection [prescribing information]. Horsham, PA: Janssen Biotech; June 2018.
2. de Vries HS, van Oijen MG, Driessen RJ, et al. Appropriate infliximab infusion dosage and monitoring: results of a panel meeting of rheumatologists, dermatologists and gastroenterologists. *Br J Clin Pharmacol.* 2011;71(1):7-19.
3. Lipsky PE, van der Heijde DM, St Clair EW, et al; for the Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. Infliximab and methotrexate in the treatment of rheumatoid arthritis. *N Engl J Med*. 2000;343:1594-1602.
4. Maini R, St Clair EW, Breedveld F, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. *Lancet*. 1999;354:1932-1939.
5. Maini RN, Breedveld FC, Kalden JR, et al. Sustained improvement over two years in physical function, structural damage, and signs and symptoms among patients with rheumatoid arthritis treated with infliximab and methotrexate. *Arthritis Rheum.* 2004;50:1051-1065.
6. St Clair EW, van der Heijde DM, Smolen JS, et al. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. *Arthritis Rheum.* 2004;50:3432-3443.
7. Targan SR, Hanauer SB, van Deventer SJ, et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. *N Engl J Med*. 1997;337:1029-1035.
8. Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the Accent I randomized trial. *Lancet*. 2002;359:1541-1549.
9. Hyams J, Crandall W, Kugathasan S, et al; REACH Study Group. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. *Gastroenterology*. 2007;132:863-873.
10. Present DH, Rutgeerts P, Targan S, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. *N Engl J Med.* 1999;340:1398-1405.
11. Sands BE, Anderson FH, Bernstein CN, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med.* 2004;350:876-885.
12. van der Heijde D, Dijkmans B, Geusens P, et al; Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy Study Group. Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomized, placebo-controlled trial (ASSERT). *Arthritis Rheum.* 2005;52:582-591.

13. Antoni C, Krueger GG, de Vlam K, et al; IMPACT 2 Trial Investigators. Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. *Ann Rheum Dis.* 2005;64:1150-1157.
14. Reich K, Nestle FO, Papp K, et al; EXPRESS study investigators. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. *Lancet*. 2005;366:1367-1374.
15. Reich K, Nestle FO, Papp K, et al. Improvement in quality of life with infliximab induction and maintenance therapy in patients with moderate-to-severe psoriasis: a randomized controlled trial. *Br J Dermatol*. 2006;154:1161-1168.
16. Menter A, Feldman SR, Weinstein GD, et al. A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. *J Am Acad Dermatol.* 2007;56:31.e1-15.
17. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med.* 2005;353:2462-2476.
18. Singh JA, Saag KG, Bridges SL Jr, et al. 2015 American College of Rheumatology Guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatol*. 2016;68(1):1-26.
19. Ward MM, Deodhar A, Akl EA, et al. American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network 2015 Recommendations for the treatment of ankylosing spondylitis and nonradiographic axial spondyloarthritis. *Arthritis Rheumatol*. Braun J, van den Berg R, Baraliakos X, et al. 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. *Ann Rheum Dis*. 2011;70(6):896-904.
20. van den Berg R, Baraliakos X, Braun J, van der Heijde D. First update of the current evidence for the management of ankylosing spondylitis with non-pharmacological treatment and non-biologic drugs: a systematic literature review for the ASAS/EULAR management recommendations in ankylosing spondylitis. *Rheumatology (Oxford).* 2012;51(8):1388-1396.
21. van der Heijde D, Sieper J, Maksymowych WP, et al. 2010 Update of the international ASAS recommendations for the use of anti-TNF agents in patients with axial spondyloarthritis. *Ann Rheum Dis*. 2011;70(6):905-908.
22. Baraliakos X, van den Berg R, Braun J, van der Heijde D. Update of the literature review on treatment with biologics as a basis for the first update of the ASAS/EULAR management recommendations of ankylosing spondylitis. *Rheumatology (Oxford)*. 2012;51(8):1378-1387.
23. Regueiro M, Schraut W, Baidoo L, et al. Infliximab prevents Crohn's disease recurrence after ileal resection. *Gastroenterology.* 2009;136(2):441-450.
24. Yamamoto T, Umegae S, Matsumoto K. Impact of infliximab therapy after early endoscopic recurrence following ileocolonic resection of Crohn's disease: a prospective pilot study. *Inflamm Bowel Dis.* 2009;15(10):1460-1466.
25. Sakuraba A, Sato T, Matsukawa H, et al. The use of infliximab in the prevention of postsurgical recurrence in polysurgery Crohn's disease patients: a pilot open-labeled prospective study. *Int J Colorectal Dis*. 2012;27(7):947-952
26. Sorrentino D, Terrosu G, Paviotti A, et al. Early diagnosis and treatment of postoperative endoscopic recurrence of Crohn's disease: partial benefit by infliximab--a pilot study. *Dig Dis Sci*. 2012;57(5):1341-1348.
27. 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..
28. Hsu S, Papp KA, Lebwohl MG, et al. Consensus guidelines for the management of plaque psoriasis. *Arch Dermatol*. 2012;148(1):95-102.
29. American Academy of Dermatology Work Group, Menter A, Korman NJ, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 6. Guidelines of care for the treatment of psoriasis and psoriatic arthritis: case-based presentations and evidence-based conclusions. *J Am Acad Dermatol*. 2011;65(1):137-174.
30. Gossec L, Smolen JS, Ramiro S, et al. European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. *Ann Rheum Dis.* 2016;75(3):499-510.
31. Coates LC, Kavanaugh A, Mease PJ, et al. Group for research and assessment of psoriasis and psoriatic arthritis: treatment recommendations for psoriatic arthritis 2015. *Arthritis Rheumatol.* 2016;68(5):1060-1071.
32. Nattiv R, Wojcicki JM, Garnett EA, et al. High-dose infliximab for treatment of pediatric ulcerative colitis: a survey of clinical practice. *World J Gastroenterol*. 2012;18(11):1229-1234.
33. Ferrante M, D'Haens G, Dewit O, et al. Efficacy of infliximab in refractory pouchitis and Crohn's disease-related complications of the pouch: a Belgian case series. *Inflamm Bowel Dis*. 2010;16(2):243-249.
34. Pardi DS, D'Haens G, Shen B, et al. Clinical guidelines for the management of pouchitis. *Inflamm Bowel Dis.* 2009;15(9):1424-1431.
35. Kornbluth A, Sachar DB; Practice Parameters Committee of the American College of Gastroenterology. Ulcerative colitis practice guidelines in adults: American College of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol*. 2010;105(3):501-523.
36. Sfikakis PP, Markomichelakis N, Alpsoy E, et al. Anti-TNF therapy in the management of Behcet's disease--review and basis for recommendations. *Rheumatology (Oxford).* 2007;46:736-741.
37. 2016;68(2):282-298.

38. Calvo-Río V, Blanco R, Beltrán E, et al. Anti-TNF-α therapy in patients with refractory uveitis due to Behçet's disease: a 1-year follow-up study of 124 patients. *Rheumatology (Oxford).* 2014;53(12):2223-2231.
39. 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.
40. 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.
41. Yang J, Cheuk DK, Ha SY, et al. Infliximab for steroid refractory or dependent gastrointestinal acute graft-versus-host disease in children after allogeneic hematopoietic stem cell transplantation. *Pediatr Transplant.* 2012;16(7):771-778.
42. Hamadani M, Hofmeister CC, Jansak B, et al. Addition of infliximab to standard acute graft-versus-host disease prophylaxis following allogeneic peripheral blood cell transplantation. *Biol Blood Marrow Transplant.* 2008;14:783-789.
43. Jacobsohn DA, Hallick J, Anders V, et al. Infliximab for steroid-refractory acute GVHD: a case series. *Am J Hematol.* 2003;74:119-124.
44. Sleight BS, Chan KW, Braun TM, et al. Infliximab for GVHD therapy in children. *Bone Marrow Transplant.* 2007;40:473-480.
45. Jacobsohn DA, Vogelsang GB. Anti-cytokine therapy for the treatment of graft-versus-host disease. *Curr Pharm Des.* 2004;10:1195-1205.
46. Patriarca F, Sperotto A, Damiani D, et al. Infliximab treatment for steroid-refractory acute graft-versus-host disease. *Haematologica.* 2004;89:1352-1359.
47. Grant A, Gonzalez T, Montgomery MO, et al. Infliximab therapy for patients with moderate to severe hidradenitis suppurativa: a randomized, double-blind, placebo-controlled crossover trial. *J Am Acad Dermatol.* 2010;62(2):205-217.
48. Sullivan TP, Welsh E, Kerdel FA, et al. Infliximab for hidradenitis suppurativa. *Br J Dermatol.* 2003;149:1046-1049.
49. Fardet L, Dupuy A, Kerob D, et al. Infliximab for severe hidradenitis suppurativa: transient clinical efficacy in 7 consecutive patients. *J Am Acad Dermatol.* 2007;56:624-628.
50. Haslund P, Lee RA, Jemec GB. Treatment of hidradenitis suppurativa with tumour necrosis factor-alpha inhibitors. *Acta Derm Venereol.* 2009;89(6):595-600.
51. Papadakis KA, Treyzon L, Abreu MT, et al. Infliximab in the treatment of medically refractory indeterminate colitis. *Aliment Pharmacol Ther.* 2003;18:741-747.
52. 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.
53. Ruperto N, Lovell DJ, Cuttica R, et al; Paediatric Rheumatology International Trials Organisation; Pediatric Rheumatology Collaborative Study Group. A randomized, placebo-controlled trial of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis. *Arthritis Rheum.* 2007;56:3096-3106.
54. Ruperto N, Lovell DJ, Cuttica R, et al. Long-term efficacy and safety of infliximab plus methotrexate for the treatment of polyarticular course juvenile rheumatoid arthritis: findings from an open-label treatment extension. *Ann Rheum Dis.* 2010;69(4):718-722.
55. Beukelman T, Patkar NM, Saag KG, et al. 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. *Arthritis Care Res (Hoboken).* 2011;63(4):465-482.
56. Lahdenne P, Vahasalo P, Honkanen V. Infliximab or etanercept in the treatment of children with refractory juvenile idiopathic arthritis: an open label study. *Ann Rheum Dis.* 2003;62:245-247.
57. Gerloni V, Pontikaki I, Gattinara M, et al. Efficacy of repeated intravenous infusions of an anti-tumor necrosis factor alpha monoclonal antibody, infliximab, in persistently active, refractory juvenile idiopathic arthritis: results of an open-label prospective study. *Arthritis Rheum.* 2005;52:548-553.
58. Tse SM, Burgos-Vargas R, Laxer RM. Anti-tumor necrosis factor alpha blockade in the treatment of juvenile spondylarthropathy. *Arthritis Rheum.* 2005;52:2103-2108.
59. 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.
60. Keystone EC. The utility of tumour necrosis factor blockade in orphan diseases. *Ann Rheum Dis.* 2004;63(Suppl 2):ii79-ii83.
61. Dabade TS, Davis MD. Diagnosis and treatment of the neutrophilic dermatoses (pyoderma gangrenosum, Sweet's syndrome). *Dermatol Ther.* 2011;24(2):273-284.
62. Brooklyn T, Dunnill G, Probert C. Diagnosis and treatment of pyoderma gangrenosum. *BMJ.* 2006;333(7560):181-184.
63. Reichrath J, Bens G, Bonowitz A, et al. Treatment recommendations for pyoderma gangrenosum: an evidence-based review of the literature based on more than 350 patients. *J Am Acad Dermatol.* 2005;53:273-283.
64. Regueiro M, Valentine J, Plevy S, et al. Infliximab for treatment of pyoderma gangrenosum associated with inflammatory bowel disease. *Am J Gastroenterol.* 2003;98:1821-1826.

65. Brooklyn TN, Dunnill GS, Shetty A, et al. Infliximab for the treatment of pyoderma gangrenosum: a randomised, double-blind placebo-controlled trial. *Gut.* 2006;55:505-509.
66. Agarwal A, Andrews JM. Systematic review: IBD-associated pyoderma gangrenosum in the biologic era, the response to therapy. *Aliment Pharmacol Ther.* 2013;38(6):563-572.
67. Maneiro JR, Salgado E, Gomez-Reino JJ, et al. Efficacy and safety of TNF antagonists in sarcoidosis: data from the Spanish registry of biologics BIOBADASER and a systematic review. *Semin Arthritis Rheum.* 2012;42(1):89-103.
68. Pritchard C, Nadarajah K. Tumour necrosis factor alpha inhibitor treatment for sarcoidosis refractory to conventional treatments: a report of five patients. *Ann Rheum Dis.* 2004;63:318-320.
69. Sweiss NJ, Welsch MJ, Curran JJ, et al. Tumor necrosis factor inhibition as a novel treatment for refractory sarcoidosis. *Arthritis Rheum.* 2005;53:788-791.
70. Doty JD, Mazur JE, Judson MA. Treatment of sarcoidosis with infliximab. *Chest.* 2005;127:1064-1071.
71. Saleh S, Ghodsian S, Yakimova V, et al. Effectiveness of infliximab in treating selected patients with sarcoidosis. *Respir Med.* 2006;100:2053-2059.
72. Vargas DL, Stern BJ. Neurosarcoidosis: diagnosis and management. *Semin Respir Crit Care Med.* 2010;31(4):419-427.
73. Rossman MD, Newman LS, Baughman RP, et al. A double-blinded, randomized, placebo-controlled trial of infliximab in subjects with active pulmonary sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis.* 2006;23(3):201-208.
74. Croft AP, Situnayake D, Khair O, et al. Refractory multisystem sarcoidosis responding to infliximab therapy. *Clin Rheumatol.* 2012;31(6):1013-1018.
75. Baughman RP, Drent M, Kavuru M, et al; Sarcoidosis Investigators. Infliximab therapy in patients with chronic sarcoidosis and pulmonary involvement. *Am J Respir Crit Care Med.* 2006;174:795-802.
76. Judson MA, Baughman RP, Costabel U, et al; Centocor T48 Sarcoidosis Investigators. Efficacy of infliximab in extrapulmonary sarcoidosis: results from a randomized trial. *Eur Respir J.* 2008;31:1189-1196.
77. Haibel H, Rudwaleit M, Listing J, et al. Efficacy of adalimumab in the treatment of axial spondylarthritis without radiographically defined sacroiliitis: results of a twelve-week randomized, double-blind, placebo-controlled trial followed by an open-label extension up to week fifty-two. *Arthritis Rheum.* 2008;58:1981-1991.
78. Doctor P, Sultan A, Syed S, et al. Infliximab for the treatment of refractory scleritis. *Br J Ophthalmol.* 2010;94(5):579-583.
79. Murphy CC, Ayliffe WH, Booth A, et al. Tumor necrosis factor alpha blockade with infliximab for refractory uveitis and scleritis. *Ophthalmology.* 2004;111(2):352-356.
80. Galor A, Perez VL, Hammel JP, Lowder CY. Differential effectiveness of etanercept and infliximab in the treatment of ocular inflammation. *Ophthalmology.* 2006;113(12):2317-2323.
81. Smith JR, Levinson RD, Holland GN, et al. Differential efficacy of tumor necrosis factor inhibition in the management of inflammatory eye disease and associated rheumatic disease. *Arthritis Rheum.* 2001;45(3):252-257.
82. Sen HN, Sangave A, Hammel K, et al. Infliximab for the treatment of active scleritis. *Can J Ophthalmol.* 2009;44(3):e9-e12.
83. Thomas JW, Pflugfelder SC. Therapy of progressive rheumatoid arthritis-associated corneal ulceration with infliximab. *Cornea.* 2005;24(6):742-744.
84. 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.
85. Pouchot J, Arlet JB. Biological treatment in adult-onset Still's disease. *Best Pract Res Clin Rheumatol.* 2012;26(4):477-487.
86. Kontzias A, Efthimiou P. Adult-onset Still's disease: pathogenesis, clinical manifestations and therapeutic advances. *Drugs.* 2008;68:319-337.
87. Rudwaleit M, van der Heijde D, Landewé R, Akkoc N, et al. The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. *Ann Rheum Dis.* 2011;70(1):25-31.
88. Reveille JD. Spondylitis. American College of Rheumatology Web site. Updated November 2013. Available at: http://www.rheumatology.org/I-Am-A/Patient-Caregiver/Diseases-Conditions/Spondyloarthritis. Accessed on July 27, 2018.
89. National Ankylosing Spondylitis Society. Axial spondyloarthritis. National Ankylosing Spondylitis Society Web site. Updated April 19, 2016. Available at: https://nass.co.uk/.. Accessed on July 27, 2018.
90. van der Heijde D, Sieper J, Maksymowych WP, et al. 2010 Update of the international ASAS recommendations for the use of anti-TNF agents in patients with axial spondyloarthritis. *Ann Rheum Dis.* 2011;70(6):905-908.
91. Servat JJ, Mears KA, Black EH, Huang JJ. Biological agents for the treatment of uveitis. *Expert Opin Biol Ther.* 2012;12(3):311-328.
92. Sobrin L, Kim EC, Christen W, et al. Infliximab therapy for the treatment of refractory ocular inflammatory disease. *Arch Ophthalmol.* 2007;125:895-900.
93. Furst DE, Keystone EC, Braun J, et al. Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2010. *Ann Rheum Dis.* 2011;70 Suppl 1:i2-36.

94. Dastmalchi, M, Grundtman, C, Alexanderson, H, et al. A high incidence of disease flares in an open pilot study of infliximab in patients with refractory inflammatory myopathies. *Ann Rheum Dis.* 2008;67:1670-1677.
95. Mukhtyar C, Guillevin L, Cid MC, et al. EULAR recommendations for the management of large vessel vasculitis. *Ann Rheum Dis*. 2009;68(3):318-323.
96. Osman M, Pagnoux C, Dryden DM, et al. The role of biological agents in the management of large vessel vasculitis (LVV): a systematic review and meta-analysis. *PLoS One*. 2014 Dec 17;9(12):e115026. Christophi GP, Ciorba MA. Lower Dose Infliximab for Ulcerative Colitis: How Low Can We Go and How Much Can be Saved? *J Clin Gastroenterol*. 2015;49(7):539-540.
97. Tayer-Shifman OE, Ilan O, Tovi H, Tal Y. Cogan's Syndrome – Clinical Guidelines and Novel Therapeutic Approaches. *Clin Rev Allergy Immunol*. 2014;47(1):65-72.
98. Hoffman GS, Merkel PA, Brasington RD, et al. Anti-tumor necrosis factor therapy in patients with difficult to treat Takayasu arteritis. *Arthritis Rheum.* 2004;50:2296-2304.
99. Mekinian A, Néel A, Sibilia J, et al. Efficacy and tolerance of infliximab in refractory Takayasu arteritis: French multicentre study. *Rheumatology (Oxford)*. 2012;51(5):882-886.
100. Buonuomo PS, Bracaglia C, Campana A, et al. Infliximab therapy in pediatric Takayasu's arteritis: report of two cases. *Rheumatol Int.* 2011;31(1):93-95.
101. Molloy ES, Langford CA, Clark TM, et al. Anti-tumor necrosis factor therapy in patients with refractory Takayasu's arteritis: long-term follow-up. *Ann Rheum Dis.* 2008;67(11):1567-1569.
102. Schmidt J, Kermani TA, Bacani AK, et al. Tumor necrosis factor inhibitors in patients with Takayasu arteritis: experience from a referral center with long-term followup. *Arthritis Care Res (Hoboken).* 2012;64(7):1079-1083.
103. Keystone EC. The utility of tumour necrosis factor blockade in orphan diseases. *Ann Rheum Dis.* 2004;63(Suppl 2):ii79-ii83.
104. Lamprecht P, Voswinkel J, Lilienthal T, et al. Effectiveness of TNF-alpha blockade with infliximab in refractory Wegener's granulomatosis. *Rheumatology (Oxford).* 2002;41:1303-1307.
105. Booth A, Harper L, Hammad T, et al. Prospective study of TNF-alpha blockade with infliximab in anti-neutrophil cytoplasmic antibody-associated systemic vasculitis. *J Am Soc Nephrol.* 2004;15:717-721.
106. Samuels J, Spiera R. Newer therapeutic approaches to the vasculitides: biologic agents. *Rheum Dis Clin North Am.* 2006;32:187-200.
107. Bartolucci P, Ramanoelina J, Cohen P, et al. Efficacy of the anti-TNF-alpha antibody infliximab against refractory systemic vasculitides: an open pilot study on 10 patients. *Rheumatology (Oxford).* 2002;41:1126-1132.
108. Salvarani C, Macchioni P, Manzini C, et al. Infliximab plus prednisone or placebo plus prednisone for the initial treatment of polymyalgia rheumatica: a randomized trial. *Ann Intern Med.* 2007;146:631-639.
109. Luqmani R. Treatment of polymyalgia rheumatica and giant cell arteritis: are we any further forward? *Ann Intern Med.* 2007;146:674-676.
110. Janta I, Martínez-Estupiñán L, Valor L, et al. Comparison between full and tapered dosages of biologic therapies in psoriatic arthritis patients: clinical and ultrasound assessment. *Clin Rheumatol.* 2015;34(5):935-942.
111. Plasencia C, Kneepkens EL, Wolbink G, et al. Comparing tapering strategy to standard dosing regimen of tumor necrosis factor inhibitors in patients with spondyloarthritis in low disease activity. *J Rheumatol.* 2015;42(9):1638-1646.
112. Jiang XL, Cui HF, Gao J, Fan H. Low-dose infliximab for induction and maintenance treatment in Chinese patients with moderate to severe active ulcerative colitis. *J Clin Gastroenterol.* 2015;49(7):582-588.
113. Závada J, Uher M, Sisol K, et al. A tailored approach to reduce dose of anti-TNF drugs may be equally effective, but substantially less costly than standard dosing in patients with ankylosing spondylitis over 1 year: a propensity score-matched cohort study. *Ann Rheum Dis.* 2016;75(1):96-102.
114. Suhler EB, Smith JR, Wertheim MS, et al. A prospective trial of infliximab therapy for refractory uveitis: preliminary safety and efficacy outcomes. *Arch Ophthalmol.* 2005;123:903-912.
115. Xeljanz® tablets [prescribing information]. New York, NY: Pfizer Inc; February 2016.
116. Christophi GP, Ciorba MA. Lower dose infliximab for ulcerative colitis: how low can we go and how much can be saved? *J Clin Gastroenterol*. 2015;49(7):539-540.
117. Inflectra™ injection for IV use [prescribing information]. Lake Forest, IL: Hospira/Pfizer; April 2016.
118. van der Heijde D, Ramiro S, Landewé R, et al. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. *Ann Rheum Dis.* 2017;76(6):978-991.
119. Renflexis injection for IV use [prescribing information]. Whitehouse Station, NJ: Samsung Bioepis/Merck; April 2017.

Other References Utilized

- de Menthon M, Cohen P, Pagnoux C, et al. Infliximab or rituximab for refractory Wegener's granulomatosis: long-term follow up. A prospective randomised multicentre study on 17 patients. *Clin Exp Rheumatol*. 2011;29(1 Suppl 64):S63-71.
- Heiligenhaus A, Michels H, Schumacher C, et al. Evidence-based, interdisciplinary guidelines for anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis. *Rheumatol Int.* 2012;32(5):1121-1133.
- Bae YS, Van Voorhees AS, Hsu S, et al. Review of treatment options for psoriasis in pregnant or lactating women: from the Medical Board of the National Psoriasis Foundation. *J Am Acad Dermatol*. 2012;67(3):459-477.
- Smolen JS1, Landewé R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis*. 2014;73(3):492-509.
- Gecse KB, Bemelman W, Kamm MA, et al. A global consensus on the classification, diagnosis and multidisciplinary treatment of perianal fistulising Crohn's disease. *Gut*. 2014;63(9):1381-1392.
- De Cassan C, Bodini G, Savarino E. Prevention of Crohn's disease recurrence after surgery: on the road to recovery. *Clin Gastroenterol Hepatol*. 2014;12(8):1406.
- Nash P, Lubrano E, Cauli A, et al. Updated guidelines for the management of axial disease in psoriatic arthritis. *J Rheumatol.* 2014;41(11):2286-9228.
- Andonopoulos AP, Meimaris N, Daoussis D, et al. Experience with infliximab (anti-TNF alpha monoclonal antibody) as monotherapy for giant cell arteritis. *Ann Rheum Dis.* 2003;62:1116.
- Cantini F, Niccoli L, Salvarani C, et al. Treatment of longstanding active giant cell arteritis with infliximab: report of four cases. *Arthritis Rheum.* 2001;44:2933-2935.
- Hoffman GS, Cid MC, Rendt-Zagar KE, et al; Infliximab-GCA Study Group. Infliximab for maintenance of glucocorticosteroid-induced remission of giant cell arteritis: a randomized trial. *Ann Intern Med.* 2007;146:621-630.

FOR MEDICAL BENEFIT COVERAGE REQUESTS:

MMO Site of Care Medical Necessity Criteria:

- Medications listed in this policy will be administered in a place of service that is a non-hospital facility based location (i.e., home infusion provider, provider's office, free-standing ambulatory infusion center) unless *at least one* of the following are met[†]:

    1. Age less than 18* years; or
    2. Clinically unstable based upon documented medical history (e.g., patient is hemodynamically unstable); or
    3. History of a severe adverse event from previous administration of the prescribed medication; or
    4. Requested medication is being administered as follows:
        - part of a chemotherapy regimen (e.g., anti-neoplastic agent, colony stimulating factor, erythropoiesis-stimulating agent, anti-emetic) for treatment of cancer; or
        - administered with dialysis; or
    5. Physical or cognitive impairment and caregiver is not available to assist with safe administration of prescribed medication in the home; or
    6. Up to 3 doses of medication or re-initiation after at least 12 months; or
    7. Experiencing adverse events that are not managed by premedication or resources available at a non-hospital facility based location.

* Effective 01/01/2019, age criterion applies to 18 years of older. Age at original effective date (03/01/2016) was 21 years or older.
†This criterion does not apply to Medicare or Medicare Advantage members.

Prior approval is required for HCPCS Code J1745, Q5103, Q5104, Q5109

HCPCS Code(s):

J1745	Injection, infliximab, excludes biosimilar, 10 mg
Q5103	Injection, infliximab-dyyb, biosimilar, (inflectra), 10 mg
Q5104	Injection, infliximab-abda, biosimilar, (renflexis), 10 mg
Q5109	Injection, infliximab-qbtx, biosimilar, (ixifi), 10 mg (effective 1/1/19)