WellMed Doctors helping patients for more than 25 years	**Effective Date: 04/05/2023**	**Revision Date(s):** 10/4/17, 12/14/17, 12/17/18, 01/07/20, 05/01/20, 12/05/20, 12/16/21, 12/15/22, 03/10/23
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Policy Number: 024.009

Title: Coverage Determination Policy for: Infliximab & Biosimilars

- **Infliximab (Remicade), Infliximab-dyyb (Inflectra), Infliximab-abda (Renflexis), Infliximab-axxq (Avsola), Infliximab-qbtx (Ixifi)**

Regions: ☒ **Texas** ☐ **Florida** ☐ **Indiana** ☐ **New Jersey** ☒ **New Mexico**

Impacted Areas:

- ☒ Network Management/Provider Services
- ☐ Member services
- ☐ Quality Management
- ☐ Credentialing
- ☐ IT
- ☐ Administration
- ☐ Compliance/delegation
- ☒ Utilization Management
- ☐ Case management
- ☐ Disease management
- ☒ Claims
- ☐ Human resources
- ☐ Finance
- ☒ Pharmacy
- ☐ ALL

Available LCD/NCD/LCA: None

Disclaimer:

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Coverage Policy Number: 024.009

Line of Business: Medicare Part B

Policy Type: Prior Authorization

Coverage Determination:

Step Therapy Criteria

This policy supplements the Medicare guidelines such as NCDs, LCDs, and other Medicare manuals for the purposes of determining coverage under the Part B medical benefits. This Step Therapy Policy is implemented to enforce a step therapy requirement for new starts only. This policy is not applicable to members continuing therapy within the past 365 days. Coverage is granted if Medicare Coverage requirements PLUS these step criteria are met.

Non-preferred drug(s): Remicade, Renflexis

Preferred drug(s): Inflectra, Avsola

Non-Preferred Product Step Therapy Criteria

Coverage of Remicade or Renflexis is medically necessary when **ONE** of the criteria listed under sections A, B, C or D are met:

A. Trial of at least 14 weeks of Inflectra or Avsola resulting in minimal clinical response to therapy and residual disease activity[2]

OR

B. History of intolerance or adverse event to Inflectra or Avsola

OR

C. Continuation of prior therapy within the past 365 days.

OR

D. **One** of the following:
   - Pediatric patient aged 16 years or younger
   - Patient is pregnant or breastfeeding

Coverage Policy

PLEASE NOTE: *For the remainder of the coverage policy, "infliximab" will be used to refer to all infliximab products including biosimilars.*

Prior to WellMed approval of infliximab products for all indications, **ALL** of the following criteria must be met **in addition to** any indication-specific criteria:

- Evidence of negative Tuberculosis (TB) screening test **OR c**urrently receiving treatment or completed treatment for TB
- Evidence of evaluation for Hepatitis B (HBV) infection prior to initiation of infliximab and monitoring for HBV reactivation during treatment with infliximab
- Patient does **NOT** have any other contraindications to infliximab, including but not limited to: active infection, NYHA Class III or IV congestive heart failure, hypersensitivity to , murine proteins, or any other component of the product or demyelinating disease (e.g. multiple sclerosis, optic neuritis)
- Patient is **NOT** being treated concurrently with a Biologic DMARD or Targeted Synthetic DMARD (e.g. Cimzia, Enbrel, Humira, Simponi, Actemra, Kineret, Orencia, Rituxan, Stelara, Xeljanz, and Otezla)

INITIAL/NEW REQUESTS

If the above clinical criteria and step therapy criteria are met, **INITIAL** requests for infliximab as medically necessary and appropriate based on the following indication-specific, evidence-based criteria will be approved for:

1. **Ankylosing spondylitis** when **ALL** of the following criteria are met:

   A. Diagnosis of ankylosing spondylitis (AS).

   B. Presence of active disease documented by provider (Active disease defined as Disease causing symptoms at an unacceptably bothersome level to the patient and judged by the examining clinician to be due to inflammation) as suggested by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) > 4 and spinal pain >4 (on a Visual Analog Scale [VAS] of 0-10).

   C. Failure, contraindication, or intolerance to appropriate initial therapy as follows:

      i. Active disease despite therapy with nonsteroidal anti-inflammatory drugs (NSAIDS).

      ii. Documentation of Inadequate Response (includes lack of efficacy such as BASDAI remains >4, adverse effects prohibiting further use of the drug or medical contraindications) to a 3 month trial of appropriately dosed conventional (non-biologic) therapy).

2. **Behçet's Disease (BD)** when **ALL** of the following criteria are met:

   A. Patient has diagnosis of BD with clinical manifestations such as severe ocular involvement, major organ involvement, severe gastrointestinal or neurological involvement and resistant cases of joint or mucocutaneous involvement (i.e., painful oral and genital ulcers).

   B. The patient has failed or had inadequate response to at least one initial conventional therapy (e.g., systemic corticosteroids, immunosuppressants [azathioprine, MTX, mycophenolate mofetil, cyclosporine, tacrolimus, Leukeran [chlorambucil], cyclophosphamide], interferon alfa) or Humira or Enbrel.

      i. Documentation of Inadequate Response (includes lack of efficacy, adverse effects prohibiting further use of the drug or medical contraindications) to a 3 month trial of appropriately dosed conventional therapy.

3**. Crohn's disease** when **ONE** of the following criteria are met:

A. Diagnosis of fistulizing Crohn's disease (perianal or abdominal enterocutaneous fistulas or rectovaginal fistulas) (first line therapy).

B. **ALL** of the following:

i. Diagnosis of moderately to severely active Crohn's disease (Crohn's Disease Activity Index (CDAI) ≥ 220)**.**

ii. History of inadequate response, contraindication, or intolerance to conventional therapy used at optimal dosing (e.g. sulfasalazine, mesalamine, balsalazide, prednisone, budesonide 6-mercaptopurine, azathioprine, methotrexate, adalimumab).

a. Documentation of Inadequate Response (includes lack of efficacy, adverse effects prohibiting further use of the drug or medical contraindications) to a 3 month trial of appropriately dosed conventional therapy.

4**. Hidradenitis suppurativa** when **ALL** of the following criteria are met:

A. Diagnosis of severe, refractory Hidradenitis suppurativa.

B. History of failure to systemic antibiotics **AND** surgical treatments.

i. Documentation of Inadequate Response (includes lack of efficacy, adverse effects prohibiting further use of the drug or medical contraindications) to a 3 month trial of appropriately dosed conventional therapy.

5. **Immune Checkpoint Inhibitor-Related Toxicities** when member has been receiving immune checkpoint inhibitor therapy (e.g. atezolizumab, durvalumab, nivolumab, Pembrolizumab, etc.). Refer to the table below:

	Diagnosis	Criteria for infliximab therapy
1.	Moderate (G2) or severe (G3-4) immunotherapy-related diarrhea or colitis	Inadequate response, intolerance, or contraindication to corticosteroids
2.	Severe (G3-4) immunotherapy-related pneumonitis	Lack of improvement after 48 hours of methylprednisolone
3.	Severe (G3) or life-threatening (G4) immunotherapy-related acute renal failure/elevated serum creatinine	If toxicity remains >G2 after 1 week of corticosteroids
4.	G3-4 uveitis	Member is refractory to high-dose systemic corticosteroids
5.	Severe (G3) or life-threatening (G4) myocarditis, pericarditis, arrhythmias, impaired ventricular function, or conduction abnormalities	Lack of improvement within 24 hours of starting pulse-dose methylprednisolone
6.	Severe immunotherapy-related inflammatory arthritis	If symptoms do not improve within 2 weeks of starting high-dose corticosteroids
7.	Moderate, severe, or life-threatening steroid-refractory myalgias or myositis	Member is refractory to corticosteroids therapy

And ONE of the following:

A. Patient is receiving Infliximab in combination with systemic corticosteroids

B. Patient is intolerant to systemic corticosteroid therapy

C. Authorization is for no more than 4 doses

6. **Noninfectious uveitis** when **ALL** of the following criteria are met:

A. Diagnosis of refractory noninfectious uveitis that is causing or threatening vision loss (e.g., noninfectious uveitis associated with Behçet's or Reiter's syndromes).

B. Infliximab used as ADJUNCT therapy for uveitis that is REFRACTORY to conventional therapy (e.g. Topical corticosteroids, Periocular or intraocular corticosteroids, Systemic corticosteroids, Immunosuppressive drugs, or a self-administered TNF-inhibitor (e.g. adalimumab).

7. **Plaque psoriasis** when **ALL** of the following criteria are met:

A. Diagnosis of chronic severe plaque psoriasis (i.e., extensive as evidenced by plaques covering at least 10% of the body surface and/or disabling) that requires systemic therapy. Documentation to support that the conditions is chronic, severe, extensive or disabling can include percent body surface area (BSA) affected; Psoriasis Area Severity Index (PASI) score; Psoriasis Disability Index (PDI) score; and/or results from other psoriasis assessment tool(s).

B. Patient is a candidate for systemic therapy and other systemic therapies are medically less appropriate per FDA approved labeling.

C. Patient meets one or more of the following conditions:

a) Patient has tried and failed a 3 month trial of prior treatment with psoralen-ultraviolet A light (UVA) or ultraviolet B (UVB) light therapy.

b) **One** of the following:

i. The patient has tried and failed one or more conventional systemic therapies (methotrexate, cyclosporine, Soriatane) for plaque psoriasis;

ii. Documentation of inadequate response (includes lack of efficacy, adverse effects prohibiting further use of the drug or medical contraindications) to a 3 month trial of appropriately dosed conventional therapy.

iii. Patient has a contraindication to conventional systemic therapies for psoriasis as determined by the prescribing physician.

8. **Pyoderma gangrenosum with coexisting inflammatory bowel disease** when **ALL** of the following criteria are met:

A. Patient has primary and secondary diagnosis for pyoderma gangrenosum and inflammatory bowel disease.

9**. Psoriatic arthritis** when **ALL** of the following criteria are met:

A. Diagnosis of active psoriatic arthritis (PsA)

B. Documentation of Inadequate Response (includes lack of efficacy, adverse effects prohibiting further use of the drug or medical contraindications) to a 3 month trial of appropriately dosed disease-specific conventional therapy.

10. **Reactive arthritis with Inflammatory Bowel Disease (e.g. Reiter's syndrome**) when **ALL** of the following criteria are met:

A. Diagnosis of both inflammatory bowel disease (ulcerative colitis or Crohn's disease) and arthritis.
B. History of failure, contraindication, or intolerance to **ALL** of the following: NSAID's, methotrexate, and sulfasalazine.

11**. Rheumatoid arthritis** when **ALL** of the following criteria are met:

A. Diagnosis of moderately to severely active rheumatoid arthritis (RA).
B. Patient has had an inadequate response to methotrexate alone.
C. An adequate trial of methotrexate should last a minimum of three (3) months. Infliximab without concurrent administration of methotrexate may be covered only for those cases where the patient is intolerant to methotrexate or for whom methotrexate is contraindicated.
    a) **ONE** of the following:
        i. Patient will be receiving concurrent therapy with methotrexate
        ii. History of contraindication or intolerance to methotrexate

12. **Sarcoidosis** when **ALL** of the following criteria are met:

A. Diagnosis of chronic pulmonary sarcoidosis (cases of extra-pulmonary sarcoidosis will be considered on a case by case basis).

B. History of failure, contraindication, or intolerance to corticosteroids (e.g., prednisone, methylprednisolone). An adequate trial of glucocorticoid therapy is considered to be a minimum of 10 mg of prednisone daily (or its equivalent) for at least 3 months. Intolerance to glucocorticoids side effects can include difficult to control diabetes mellitus, excessive weight gain, myopathy, or osteoporosis.

C. History of failure, contraindication, or intolerance to an adequate trial (at least 3 months) of at least **one** immunosuppressant (e.g. methotrexate, leflunomide, azathioprine, mycophenolate, cyclophosphamide).

D. Patient is **NOT** receiving infliximab in combination with either of the following:

i. Biologic DMARD (e.g. etanercept, adalimumab, certolizumab, golimumab)

ii. Janus kinase inhibitor (e.g. tofacitinib).

13. **Still's disease, Adult onset** (ASD) when **ALL** of the following criteria are met:

A. Diagnosis of Still's disease per the Yamaguchi criteria or other widely accepted diagnostic criteria for ASD.

14**. Takayasu arteritis (Aortic arch syndrome), refractory** when **ALL** of the following criteria are met:

A. Diagnosis of Takayasu arteritis.

B. REFRACTORY disease as evidenced by documentation of Inadequate Response (includes lack of efficacy, adverse effects prohibiting further use of the drug or medical contraindications) to a 3 month trial of appropriately dosed disease-specific conventional therapy (e.g. high dose corticosteroids or non-steroid immunosuppressant).

15**. Ulcerative colitis** when **ALL** of the following criteria are met:

A. Diagnosis of moderately to severely active ulcerative colitis (UC).

B. History of inadequate response, contraindication, or intolerance (e.g. sulfasalazine, balsalazide, mesalamine, corticosteroids, 6-mercaptopurine, amino salicylate, azathioprine) unless contraindication or intolerance to such therapies. Documentation of Inadequate Response (includes lack of efficacy, adverse effects prohibiting further use of the drug or medical contraindications) to a 3 month trial of appropriately dosed conventional therapy.

RENEWAL/CONTINUATION OF THERAPY REQUESTS

Renewal requests falling outside recommended dosing for the patient's indication or not meeting the criteria above will be forwarded to the Medical Director for review.

RENEWAL criteria for **Rheumatoid Arthritis**:

A. The patient has documented significant improvement with prior courses of treatment.
B. The requested dosing regimen remains within the recommended dosing parameters as listed in the dosing table.
C. To support continued use *beyond 30 weeks*, the medical record must include evidence of:
    i. at least 20% improvement in tender joint count, **AND**
    ii. at least 20% improvement in swollen joint count

RENEWAL criteria for **Crohn's disease**:

A. Retreatment will be covered when medical record substantiates that the patient had a reduction in the clinical signs and symptoms of the disease after the initial treatment. Relevant information includes the presence and severity of abdominal pain, diarrhea, extra intestinal manifestations, enterocutaneous and/or rectovaginal fistulae.
B. The requested dosing regimen remains within the recommended dosing parameters as listed in the dosing table.

RENEWAL requests for continued use of infliximab in **all other indications** will be approved if:

A. Patient has documented significant improvement with prior courses of treatment.
B. Requested dosing regimen remains within the recommended dosing parameters as listed in the dosing table.
C. Patient still meets all of the indication-specific criteria above.

Note: *Infliximab and its biosimilar are not recommended for indications not listed above in the Coverage Policy and will* ***NOT*** *be authorized. Statistically robust randomized controlled trials are needed to address the issue of whether infliximab has sufficient superiority in clinical efficacy compared to other available treatments to justify the inherent clinical risk in the use of a monoclonal antibody anti-tumor necrosis factor agent for other indications. Coverage criteria will be updated as new published data are available. Any requests for indications not listed above will be forwarded to the Medical Director for review.*

FDA Approved Indications

- Ankylosing spondylitis, Active
- Crohn's disease, Fistulizing
- Crohn's disease (Moderate to Severe), In patients with an inadequate response to conventional therapy
- Plaque psoriasis, chronic (Severe)
- Psoriatic arthritis
- Rheumatoid arthritis (Moderate to Severe), In combination with methotrexate
- Ulcerative colitis (Moderate to Severe), In patients with an inadequate response to conventional therapy

Dosing

MAX ALLOWABLE DOSING: *Doses above 10 mg/kg or with a frequency shorter than every 4 weeks will NOT be authorized.*

Indication	Dosing*
Ankylosing spondylitis	• 5 mg/kg at 0, 2 and 6 weeks, then every 6 weeks thereafter
Behçet's Disease (BD)	• 3 to 5 mg/kg at weeks 0, 2, and 6, then every 6-8 weeks thereafter • **If inadequate response after at least 2 months of therapy, dose escalation up to max of 10 mg/kg **AND/OR** decreasing dosing interval to 4-7 weeks is permissible
Crohn's disease	• 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks • **Dose escalation up to max of 10 mg/kg **AND/OR** decreasing dosing interval to 4-7 weeks is permissible in the event of loss of response • See RENEWAL limitations section
Hidradenitis suppurativa, severe, refractory	• 5 mg/kg at 0, 2, and 6 weeks • Any subsequent doses at 5 mg/kg every 6-8 weeks must be justified in medical records by positive clinical response and lack of adverse effects
Noninfectious uveitis	• 5 mg/kg at 0, 2 and 6 weeks, then every 4-8 weeks • **Dose escalation up to max of 10 mg/kg is permissible in the event of loss of response
Plaque psoriasis	• 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks thereafter
Psoriatic arthritis	• 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks thereafter • May be given with or without concomitant methotrexate
Pyoderma gangrenosum with coexisting inflammatory bowel disease	• 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks • **Dose escalation up to max of 10 mg/kg **AND/OR** decreasing dosing interval to 4-7 weeks is permissible in the event of loss of response

Reactive arthritis with inflammatory bowel Disease - off-label use	• 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks thereafter
Rheumatoid arthritis	• In conjunction with methotrexate, 3 mg/kg at 0, 2 and 6 weeks, then every 8 weeks • **Some patients may benefit from increasing the dose up to max of 10 mg/kg **AND/OR** treating as often as every 4-7 weeks per package insert. • See RENEWAL limitations section
Sarcoidosis	• 3 to 5 mg/kg at weeks 0, 2, 6, and 12 • The optimal frequency for subsequent dosing is not known
Still's disease, Adult onset	• 3 mg/kg at 0, 2 and 6 weeks, then every 8 weeks • **Some patients may benefit from increasing the dose up to max of 10 mg/kg **AND/OR** treating as often as every 4-6 weeks
Takayasu's disease, refractory	• 3 to 5 mg/kg every 4-8 weeks
Ulcerative colitis	• 5 mg/kg at weeks 0, 2, 6, then every 8 weeks thereafter
Immune Checkpoint Inhibitor-Related Toxicities	• 5 mg/kg • Additional doses should be administered 2 and 6 weeks after initial dose if required

***Lowest effective dose should be utilized; Doses >5 mg/kg are CONTRAINDICATED in moderate to severe heart failure (NYHA Class III or IV)*

****Medical records for patients with an incomplete response at initial doses must contain and substantiate the rationale for going to the higher doses (e.g. 10 mg/kg) or shorter frequencies (e.g. every 4 weeks)*

General Background

Infliximab is a chimeric human/mouse monoclonal antibody (cA2) that demonstrates anti-tumor necrosis factor alfa (TNF-alfa) activity. TNF-alfa is a key mediator of mucosal inflammation and can be neutralized by cA2 antibody, which binds to the soluble and transmembrane forms and blocks binding of TNF-alfa with its receptors. Based on this mechanism of action, infliximab can help reduce signs and symptoms of certain inflammatory conditions in which TNF activity is correlated with disease severity, including ankylosing spondylitis, Crohn's disease, plaque psoriasis, rheumatoid arthritis, ulcerative colitis, and other rare inflammatory conditions.

Infliximab has FDA Black Box safety warnings for serious infections and malignancy. Patients being treated with infliximab are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were on concomitant immunosuppressants. Reported infections include active tuberculosis, invasive fungal infections, and infections due to opportunistic pathogens including Legionella and Listeria. The risks and benefits of treatment with infliximab should be considered carefully before initiating treatment in patients with chronic or recurrent infections. Patients should be monitored closely for signs and symptoms of infection during and after treatment with infliximab.

The concurrent administration of live vaccines and therapeutic infectious agents (such as live attenuated bacteria) with Infliximab is not recommended due to increased infection risk.

Cases of cardiovascular and cerebrovascular reaction, lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers including infliximab. Also, post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL) have been reported in patients treated with TNF blockers including infliximab. These cases have had an aggressive disease course and have been fatal. Almost all of the patients had received azathioprine or 6-mercaptopurine concomitantly with a TNF-blocker. Most of the reported infliximab cases occurred in adolescent and young adult males with Crohn's disease or ulcerative colitis. Recent post marketing cases of acute hepatic failure, cholestatic hepatitis (including vanishing bile duct syndrome) and hepatotoxicity (idiosyncratic) have been reported.

Medicare does not have a National Coverage Determination (NCD) for Infliximab. Local Coverage Determinations (LCDs) do not exist for Texas, however LCD and LCA are available for other states and have been adopted where applicable. [32]

Clinical Evidence

A Danish study published in the May 4, 2017 issue of *Annals of Rheumatic Diseases* examined 802 patients who were switched from Remicade to infliximab biosimilar Inflectra after 1 year of follow up. The patients were 51% women, had a median age of 55 years, and had diagnoses of rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis. The average treatment duration with Remicade® prior to switching was 6.8 years (range 4.3-9.5 years). The authors concluded that switching to the biosimilar does not appear to have a negative effect on inflammatory arthritis disease activity. Absolute retention rates and flare rates were also similar.

HCPCS Code

Coding Clarification: HCPCS code Q5109 is provided for informational purposes only.

Ixifi (infliximab-qbtx) is currently unavailable in the USA.

HCPCS codes	Description
J1745	Injection, infliximab, (Remicade), 10 mg
Q5103*	Injection, infliximab-dyyb, biosimilar, (Inflectra), 10 mg
Q5104	Injection, infliximab-abda, biosimilar, (Renflexis), 10 mg
Q5121*	Injection, infliximab-axxq, biosimilar, (Avsola), 10mg
Q5109	Injection, infliximab-qbtx, biosimilar, (Ixifi), 10 mg

Preferred Drug(s)/Product(s)

Acronyms

(NCDs) = National Coverage Determinations

(LCDs) = Local Coverage Determinations

(cA2) = Chimeric human/mouse monoclonal antibody

(TNF-alfa) = Tumor necrosis factor alfa

(HSTCL) = Hepatosplenic T-cell lymphoma

(TB) = Tuberculosis

(HBV) = Hepatitis B

(AS) = Ankylosing spondylitis

(nr-axSpA) = Non-radiographic axial spondyloarthritis

(SpA) = Peripheral spondyloarthritis

(DMARD) = Traditional disease-modifying antirheumatic drug

(NYHA) = New York Heart Association

(BASDAI) = Bath Ankylosing Spondylitis Disease Activity Index

(ASDAS) = Ankylosing Spondylitis Disease Activity Score

(NSAIDS) = Nonsteroidal anti-inflammatory drugs

(BD) = Behçet's Disease

(CDAI) = Crohn's Disease Activity Index

(BSA) = Body surface area

(PASI) = Psoriasis Area Severity Index

(PDI) = Psoriasis Disability Index

(MTX) = Methotrexate

(PUVA) = Ultraviolet A light

(ASD) = Still's disease, Adult onset

(UC) = Ulcerative colitis

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