Children's Hospital and Health System
Chorus Community Health Plan Policy and Procedure

This policy applies to the following entity(s):

☐ CHW – Milwaukee	☐ CHW - Fox Valley
☐ CHHS Foundation	☐ CHW - Surgicenter
☐ CHW – Community Services Division	☒ Chorus Community Health Plan
☐ Children's Medical Group - Primary Care	☐ Children's Specialty Group
☐ Children's Medical Group - Urgent Care	☐ CHHS Corporate Departments

Medical Utilization Management Policy

SUBJECT: INFLIXIMAB (AVSOLA, INFLECTRA, REMICADE, RENFLEXIS)

INCLUDED PRODUCT(S):

Medicaid	**Individual and Family**
☒ BadgerCare Plus	☒ Commercial
☒ Care4Kids Program	☒ Marketplace

PURPOSE OR DESCRIPTION:

The purpose of this policy is to define criteria for the medically necessary use of infliximab (Avsola, Inflectra, Remicade, Renflexis).

***** *This policy is adapted from MCG guideline A-0308 (infliximab) with one additional off-label indication.*

FDA Approved Indication(s):

Avsola, Inflectra, infliximab (unbranded), Remicade, Renflexis

- **Crohn's disease**:
  - reducing signs and symptoms, and inducing and maintaining clinical remission in adult patients with moderate to severe active disease who have had an inadequate response to conventional therapy

    - reducing the number of draining enterocutaneous and rectovaginal fisulas, maintaining fistula closure in adult patients with fistulizing disease
- **Pediatric Crohn's disease**: reducing signs and symptoms, and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderate to severe active disease who have had an inadequate response to conventional therapy
- **Ulcerative colitis**: reducing signs and symptoms, and inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderate to severe active disease who have had an inadequate response to conventional therapy
- **Pediatric ulcerative colitis**: reducing signs and symptoms, and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderate to severe active disease who have had an inadequate response to conventional therapy
- **Rheumatoid arthritis in combination with methotrexate**: reducing signs and symptoms, and inhibiting the progression of structural damage, and improving physical function in adult patients with moderate to severe active disease
- **Ankylosing spondylitis**: reducing signs and symptoms in adult patients with active disease
- **Psoriatic arthritis**: reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in adult patients
- **Plaque psoriasis**: treatment of adult patients with chronic severe (i.e., extensive and/or disabling) plaque psoriasis who are candidates for systemic therapy, when other systemic therapies are medically less appropriate

POLICY:

- Infliximab may be indicated when **ALL** of the following are present (1):
    - Clinical diagnosis of **1 or more** of the following:
        - Ankylosing spondylitis, as indicated by **1 or more** of the following (25)(26)(27):
            - Initial course, as indicated by **ALL** of the following[A] (34):
                - Age 18 years or older
                - Clinical evidence of ankylosing spondylitis, as indicated by **ALL** of the following (26)(29)(30)(35)(36)(37)(38):
                    - Back pain lasting 3 or more months and age of onset of 45 years or younger
                    - Classification criteria met, as indicated by **ALL** of the following:
                        - Sacroiliitis on imaging
                        - Spondylarthritis signs and symptoms, as indicated by **1 or more** of the following:
                            - Arthritis
                            - Dactylitis
                            - Elevated C-reactive protein
                            - Enthesitis (eg, inflammation of Achilles tendon insertion)
                            - Family history of spondylarthritis

        - HLA-B27
        - Inflammatory bowel disease (Crohn's disease, ulcerative colitis)
        - Limited chest expansion
        - Morning stiffness for 1 hour or more
        - Psoriasis
        - Uveitis
    - Disease activity and treatment scenario, as indicated by **1 or more** of the following:
        - Axial (spinal) disease
        - Loss of response or intolerance to treatment with tumor necrosis factor inhibitor (35)
    - Trial or intolerance of 2 or more different NSAIDs (at maximum recommended doses) over a total period of at least 4 or more weeks of therapy
- Subsequent course, as indicated by **ALL** of the following:
    - Age 18 years or older
    - Active ankylosing spondylitis
    - Favorable response to prior administration of infliximab

- Crohn disease, as indicated by **1 or more** of the following (39)(40)(41)(42)(43):
    - Initial course, as indicated by **1 or more** of the following[B] (55)(57):
        - Fistulizing Crohn's disease and **ALL** of the following (46)(64):
            - Age 18 years or older
            - Draining enterocutaneous or rectovaginal fistula
            - Duration of 3 or more months
        - Nonfistulizing Crohn's disease and **ALL** of the following:
            - Age 6 years or older (65)
            - Moderate to severe active Crohn's disease,[C] as indicated by **1 or more** of the following (40)(66):
                - Anemia
                - Dehydration
                - Elevated serum C-reactive protein level
                - Fever
                - Intermittent vomiting
                - Perianal or rectal disease on endoscopy (52)(67)
                - Weight loss of greater than 10% of body weight
            - Intolerance or inadequate response to therapy with **1 or more** of the following (54)(55):
                - 6-mercaptopurine
                - Azathioprine
                - Methotrexate

- Oral corticosteroids
- Subsequent course, as indicated by **ALL** of the following[D] (57):
  - Clinical diagnosis, as indicated by **1 or more** of the following:
    - Fistulizing Crohn's disease, and age 18 years or older
    - Nonfistulizing Crohn's disease, and age 6 years or older
  - Favorable response to prior administration of infliximab

- Immune checkpoint inhibitor (eg, atezolizumab, ipilimumab, nivolumab, pembrolizumab)-related toxicity, as indicated by **ALL** of the following[E] (72)(73):
  - Adverse effect, known or suspected, as indicated by **1 or more** of the following:
    - Enterocolitis, grade 2 or higher (i.e., 4 or more bowel movements daily, abdominal pain, nausea, vomiting)
    - Inflammatory arthritis, severe (i.e., limitation of activities of daily living, radiographic presence of joint erosions)
    - Myocarditis without reduced left ventricular ejection fraction (75)
    - Myositis, moderate to severe (i.e., pain with elevated muscle enzymes and limitation of activities of daily living)
    - Nephritis, grade 3 or higher (i.e., creatinine greater than 3 times baseline level, creatinine greater than 4 mg/dL (354 micromoles/L), dialysis needed)
    - Pneumonitis, grade 3 or higher (i.e., greater than 50% of parenchyma involved on radiologic examination, limitation of activities of daily living, oxygen required, life-threatening respiratory compromise) (76)(77)
  - Incomplete or no response to corticosteroid therapy

- Plaque psoriasis, as indicated by **1 or more** of the following (78)(79)(80):
  - Initial course, indicated by **ALL** of the following[F]:
    - Age 18 years or older
    - Moderate to severe plaque psoriasis, as indicated by **ALL** of the following (84)(87)(88)(89)(90):
      - Candidate for systemic therapy or phototherapy
      - Clinical need for systemic treatment, as indicated by **1 or more** of the following:
        - Body surface area involvement of 10% or more
        - Involvement of scalp, face, feet, hands, or genitalia that impacts member quality of life
      - Trial of other treatments to control psoriasis, as indicated by **1 or more** of the following (84)(87):
        - Immunosuppressive treatments (e.g., cyclosporine, methotrexate)

- Photochemotherapy (i.e., psoralen plus ultraviolet A therapy) (91)
- Phototherapy (i.e., ultraviolet light therapy) (91)
- Topical agents (e.g., anthralin, calcipotriene, coal tars, corticosteroids, tazarotene) (87)
- Tumor necrosis factor inhibitor (80)

- Subsequent course, as indicated by **ALL** of the following:
  - Age 18 years or older
  - Favorable response to prior administration of infliximab

- Psoriatic arthritis, as indicated by **1 or more** of the following (80)(92)(93):
  - Initial course, as indicated by **ALL** of the following[G] (99)(100):
    - Age 18 years or older
    - Active arthritis, as indicated by **1 or more** of the following:
      - Axial disease with inflammatory back pain, and trial of or intolerance to NSAIDs
      - Dactylitis[H]
      - Enthesitis[I] that is tender on examination
      - Peripheral disease with one or more tender and swollen joints, and trial of, intolerance to, or contraindication to methotrexate
    - Inadequate response, intolerance, or contraindication to 3 or more months of treatment with one or more NSAIDs
  - Subsequent course, as indicated by **ALL** of the following:
    - Age 18 years or older
    - Favorable response to prior administration of infliximab

- Rheumatoid arthritis and **1 or more** of the following (25)(102)(103)(104):
  - Initial course, as indicated by **ALL** of the following[J]:
    - Age 18 years or older
    - Inadequate response to 3 or more months of treatment with disease-modifying antirheumatic drug, including **1 or more** of the following (102)(104)(111)(116)(117):
      - Hydroxychloroquine
      - Leflunomide
      - Methotrexate
      - Sulfasalazine
      - Tumor necrosis factor inhibitor (116)(117)(118)
    - Concurrent treatment with methotrexate (119)(120)
    - Moderate to severe active rheumatoid arthritis,[K] as indicated by **1 or more** of the following (121)(122)(123):
      - Clinical Disease Activity Index[L] score greater than 10
      - Disease Activity Score[M] of 3.2 or greater

        - Patient Activity Scale[N] of 3.71 or greater
        - Patient Activity Scale-II[N] of 3.71 or greater
        - Routine Assessment of Patient Index Data 3[O] score greater than 2
        - Simplified Disease Activity Index[P] score greater than 11
    - Subsequent course, as indicated by **ALL** of the following:
        - Age 18 years or older
        - Concurrent treatment with methotrexate
        - Favorable response to prior administration of infliximab (124)
- Ulcerative colitis, as indicated by **1 or more** of the following (125)(126)(127)(128)(129):
    - Initial course, as indicated by **ALL** of the following[Q]:
        - Age 6 years or older (65)(142)(143)
        - Intolerance or inadequate response to conventional therapy with **1 or more** of the following:
            - 6-mercaptopurine
            - Azathioprine
            - Oral corticosteroids (144)
            - Salicylates
        - Moderate to severe active ulcerative colitis, as indicated by **1 or more** of the following (57)(131)(132)(145):
            - Anemia
            - Bowel movements 4 or more times per day
            - Erosions, friability, or ulceration on endoscopy
            - Urgency of defecation
            - Visible blood in stool
    - Subsequent course, as indicated by **ALL** of the following (146):
        - Age 6 years or older
        - Favorable response to prior administration of infliximab (147)
- Uveitis (noninfectious, chronic), as indicated by **ALL** of the following[R] (148)(149)(150)(151):
    - Loss of visual acuity or evidence of retinal involvement
    - Trial of systemic corticosteroids or other immunosuppressant
- Sarcoidosis and **1 or more** of the following:
    - Initial course, as indicated by **ALL** of the following:
        - **1 or more** of the following:
            - History of trial, intolerance, or contraindication to **1 or more** glucocorticoids
            - Medical need for steroid sparing therapy

        - History of trial, intolerance, or contraindication to **1 or more** conventional immunosuppressants (e.g., azathioprine, or cyclophosphamide, or methotrexate)
    - Subsequent course, as indicated by **ALL** of the following:
        - Favorable response while on therapy with infliximab
- Hepatitis B surface antigen (HBsAg) negative, or concurrent treatment with antiviral therapy[S] (158)(159)(160)
- No active infection (25)(85)(161)(162)(163)
- No concurrent treatment with other biological drug (e.g., abatacept, anakinra, or another tumor necrosis factor inhibitor) (25)
- No concurrent use of live vaccine[T] (25)(160)(164)
- No untreated latent or active tuberculosis (25)(85)(128)(159)(161)(162)

Applicable Codes:

HPCS Code:

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

Sarcoidosis focused background:

The utilization of infliximab for refractory/treatment-resistant sarcoidosis is an off-label indication that is supported by medical literature and published treatment protocols. The Foundation for Sarcoidosis Research Sarcoidosis Treatment Guidelines (FSRSTG) [4] recommend anti-TNF therapy (defined as adalimumab or infliximab) for pulmonary sarcoidosis that has not responded to corticosteroid doses of >/= to 10 mg daily of prednisone and an immunosuppressant medication. The FSRSTG recommend anti-TNF therapy for posterior uveitis or panuveitis associated with sarcoidosis for patients that have not responded to corticosteroids and an immunosuppressant. The FSRSTG recommend anti-TNF therapy for patients with mild-moderately disabling neurosarcoidosis who have not responded to corticosteroids and an immunosuppressant. The FSRSTG recommend anti-TNF therapy for patients with severely disabling neurosarcoidosis who have not responded to corticosteroids. The FSRSTG recommend anti-TNF therapy for patients with cutaneous lesions associated with sarcoidosis who have not responded to topical therapies and/or corticosteroids and/or immunosuppressants.

The European Respiratory Society (ERS) clinical practice guidelines on the treatment of sarcoidosis[5] has a conditional recommendation for the use of infliximab for cutaneous manifestations of sarcoidosis in patients that have not responded to topical steroids, oral corticosteroids, hydroxychloroquine, and methotrexate. The ERS guidelines has a conditional recommendation for infliximab in patients with pulmonary sarcoidosis who have failed glucocorticoids and immunosuppressants. The ERS guidelines recommend infliximab for cardiac sarcoidosis in patients who have not responded to glucocorticoids and an immunosuppressant. The ERS guidelines have a conditional recommendation for infliximab for

symptomatic neurosarcoidosis in patients who have failed glucocorticoids and immunosuppressants.

The use of infliximab for refractory sarcoidosis has also been demonstrated though small clinical trials, case series and case reports.[2, 3, 7, 8, 9, 10, 11, 12, 13, 14]

For background and references related to indications other than sarcoidosis see MCG guideline A-0308(AC)

References:

1. Infliximab. MCG Health Ambulatory Care Guideline A-0308(AC). MCG Health
2. Amin EN, Closser DR, Crouser ED. Current best practice in the management of pulmonary and systemic sarcoidosis. Therapeutic Advances in Respiratory Disease. 2014;8(4):111-132.
3. Baughman RP, Lower EE. Infliximab for refractory sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 2001;18(1):70-74
4. 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(7):795-802.
5. Baughman RP, Valeyre D, Korsten P, et al. ERS clinical practice guidelines on treatment of sarcoidosis. Eur Respir J. 2021;58(6):2004079.
6. Baughman RP, Culver D, Drake W, er al. Foundation for Sarcoidosis Research Sarcoidosis Treatment Guidelines.
7. Doherty CB, Rosen T. Evidence-based therapy for cutaneous sarcoidosis. Drugs. 2008;68(10):1361-83
8. Doty JD, Mazur JE, Judson MA. Treatment of sarcoidosis with infliximab. Chest. 2005;127(3):1064-71.
9. Drent M, Cremers JP, Jansen TL, Baughman RP. Practical eminence and experience-based recommendations for use of TNF-α inhibitors in sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 2014;31(2):91-107.
10. Melani AS, Bigliazzi C, Cimmino FA, Bergantini L, Bargagli E. A comprehensive review of sarcoidosis treatment for pulmonologists. Pulm Ther. 2021;7(2):325-344.
11. Sakkat A, Cox G, Khalidi N, et al. Infliximab therapy in refractory sarcoidosis: a multicenter real-world analysis. Respir Res. 2022;23(1):54.
12. Soto-Gomez N, Peters JI, Nambiar AM. Diagnosis and Management of Sarcoidosis. Am Fam Physician. 2016 May 15;93(10):840-8.
13. Ulbricht KU, Stoll M, Bierwirth J, et al. Successful tumor necrosis factor alpha blockade treatment in therapy-resistant sarcoidosis. Arthritis Rheum. 2003; 48(12):3542-3.
14. Yee AM, Pochapin MB. Treatment of complicated sarcoidosis with infliximab anti-tumor necrosis factor-alpha therapy. Ann Intern Med. 2001;135(1):27-31
15. Remicade [package insert]. Horsham, PA: Jansen Biotech, Inc.; October 2021.
16. Renflexis [package insert]. Whitehouse Station, NJ: Merck & Co., Inc..; January 2022.
17. Inflectra [package insert]. Lake Forest, IL: Hospira, a Pfizer company; April 2022.
18. Avsola [package insert]. Thousand Oaks, CA: Amgen; September 2021.