PART B DRUG MEDICAL/PHARMACY	ASPIRE HEALTH	Effective Date May 1, 2024	
	INFLIXIMAB PRODUCTS REMICADE®; INFLECTRA®; RENFLEXIS™; AVSOLA®; INFLIXIMAB* (INTRAVENOUS) ZYMFENTRA™ SC (INFLIXIMAB-DYYB)	**Policy #** Infliximab Products	
		Review Date 02/27/2024	**Applicable to:** ☑ Medicare Advantage ☐ Commercial ☐ Elevance Health HMO ☐ Blue Shield Trio
	Approver's Name & Title QI & UM Drug Subcommittee		

Aspire Health Plan applies medical drug clinical criteria as a reference for medical policy information only. Federal and state laws or requirements, contract language, and Plan benefit may take precedence over the application of these clinical criteria. Please consult the applicable certificate or contract for benefit details. This policy is subject to revision at the discretion of the Plan and is therefore subject to change. Refer to the disclaimer section below for more information.

POLICY

This policy addresses the coverage of infliximab products.

NOTE: Any U.S. Food and Drug Administration (FDA) approved and launched infliximab biosimilar product not listed by name in this policy will be considered non-preferred until reviewed by Aspire Health.

APPLICABLE HCPCS

J1745: Injection, infliximab, excludes biosimilar, 10 mg; 1 billable unit = 10 mg (Includes unbranded biologic)
Q5103: Injection, infliximab-dyyb, biosimilar, (Inflectra), 10 mg: 1 billable unit = 10 mg
Q5104: Injection, infliximab-abda, biosimilar, (Renflexis), 10 mg; 1 billable unit = 10 mg
Q5109: Injection, infliximab-qbtx, biosimilar, (Ixifi), 10 mg; 1 billable unit = 10 mg
Q5121: Injection, infliximab-axxq, biosimilar, (Avsola), 10 mg: 1 billable unit=10 mg
J3590, Q5136: Unclassified Biologics, biosimilar, (Zymfentra)

Available as:

- Remicade 100 mg single-dose vial for injection
- Infliximab 100 mg single-dose vial for injection (Unbranded biologic*)
- Inflectra 100 mg single-dose vial
- Renflexis 100 mg single-dose vial
- Avsola 100 mg single-dose vial for injection
- Zymfentra 120 mg/mL in a single-dose prefilled syringe and pen

CLINICAL CRITERIA

I. INITIAL CRITERIA

Infliximab may be authorized when the **GENERAL** and **CONDITION-SPECIFIC** criteria have been met with *documentation.

*Medical record documentation by the Prescriber / administering physician should substantiate the medical necessity for the use of Infliximab by clearly indicating the relevant clinical signs and symptoms related to the medical condition for which this drug is indicated. The documentation must also include all prior treatment regimens and the member's response to that therapy.

A. General Criteria (#1-3) applicable to ALL requests:

1. Documented diagnosis of **ONE** of the following:
    a. Ankylosing spondylitis
    b. Crohn disease
    c. Plaque psoriasis
    d. Psoriatic arthritis
    e. Rheumatoid arthritis
    f. Ulcerative colitis
    g. Immune checkpoint inhibitor-related toxicity
    h. Uveitis (noninfectious, chronic).

AND

2. Member has been evaluated/screened for the presence of the following conditions ***prior to*** initiating treatment and meets **ALL** of the following:
    a. No active infection; and
    b. No untreated active or latent tuberculosis; and
    c. No concurrent treatment with ANY of the following:
        i. Other biological agents (e.g., anakinra, abatacept, or another tumor necrosis factor inhibitor [etanercept, adalimumab, certolizumab, and golimumab] or a Janus kinase inhibitor [e.g. tofacitinib]); and
        ii. Live vaccines
    d. Hepatitis B surface antigen (HBsAg) negative; and
    e. Moderate or severe heart failure (i.e., New York Heart Association [NYHA] Functional Class III/IV) [Note: Only applies when doses >5mg/kg are used]; and
    f. Member is up-to-date with all immunizations in accordance with vaccination guidelines.

AND

3. Prescriber has assessed baseline disease severity utilizing an objective measure / tool.

AND

B. Condition-Specific Criteria (1-8)

Member meets **ONE** of the following condition-specific criteria as applicable to member's diagnosis.

1. <u>Ankylosing Spondylitis</u>
    a. Documented moderately to severely active disease; **AND**
    b. Inadequate response to at least TWO (2) non-steroidal anti-inflammatory agents (NSAIDs) (at maximum recommended doses) over a total period of FOUR (4) weeks or more, unless contraindicated.

2. Crohn Disease
    a. Documented moderate to severe disease and **ONE** of the following:
        i. Fistulizing Crohn disease
        ii. Nonfistulizing Crohn disease

    AND

    b. Inadequate response, contraindication, or ineffective response at maximum tolerated doses to conventional therapy: at least a THREE (3) month trial of oral corticosteroids or immunomodulators (e.g., azathioprine, 6-mercaptopurine, or methotrexate).

3. Immune Checkpoint Inhibitor Related Toxicity
    a. Member has been receiving therapy with an immune checkpoint inhibitor (e.g., nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab, cemiplimab, ipilimumab, dostarlimab, etc.); **AND**
    b. Adverse effect, known or suspected, as indicated by **ONE or more** of the following:
        i. Enterocolitis, grade 2 or higher (i.e., 4 or more bowel movements daily, nausea, vomiting, abdominal pain); or
        ii. Inflammatory arthritis, severe (i.e., limitation of activities of daily living, radiographic presence of joint erosions); or
        iii. Myocarditis without reduced left ventricular ejection fraction; or
        iv. Myositis, moderate to severe (i.e., pain with elevated muscle enzymes and limitation of activities of daily living); or
        v. 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]; or
        vi. 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).Incomplete or no response to corticosteroid therapy.

    AND

    c. Inadequate or no response to corticosteroid therapy.

4. Plaque Psoriasis
    a. Documented diagnosis of moderate to severe, chronic plaque psoriasis, **AND**

    b. Member is a *candidate for systemic therapy or phototherapy; **AND**

        **Contraindications to phototherapy (PUVA or UVB) include the following: Xeroderma pigmentosum; Pregnancy or lactation (PUVA only); Lupus Erythematosus; History of one of the following: photosensitivity diseases (e.g., chronic actinic dermatitis, solar urticaria), melanoma, non-melanoma skin cancer, extensive solar damage (PUVA only), treatment with arsenic or ionizing radiation; Immunosuppression in an organ transplant patient (UVB only)' Photosensitizing medications (PUVA only); Severe liver, renal, or cardiac disease (PUVA only).*

    AND

    c. Clinical need for systemic treatment, as indicated by **ONE** or more of the following:
        i. Body surface area involvement of 10% or more, or
        ii. Involvement of scalp, face, feet, hands, or genitalia that impacts patient quality of life; or
        iii. Psoriasis Area and Severity Index (PASI) score of 10 or greater.

AND

d. Failure of other treatments to control psoriasis, as documented by **ONE** or more of the following:
    i. Immunosuppressive treatments (e.g., cyclosporine, methotrexate); or
    ii. Photochemotherapy (e.g., psoralen plus ultraviolet A therapy); or
    iii. Phototherapy (e.g., psoralens with UVA light [PUVA] or UVB with coal tar or dithranol); or
    iv. Topical agents (e.g., anthralin, calcipotriene, coal tars, corticosteroids, tazarotene, (e.g., anthralin, coal tar preparations, emollients, immunosuppressives, keratolytics, retinoic acid derivatives, and/or vitamin D analogues); or
    v. Tumor necrosis factor inhibitor.

5. Psoriatic Arthritis
    a. Documented diagnosis of moderate to severe active disease; **AND**
    b. Active arthritis, as indicated by ONE (1) or more of the following:
        i. Axial disease with inflammatory back pain, and failure or intolerance of NSAIDs; or
        ii. Dactylitis; or
        iii. Enthesitis that is tender on examination; or
        iv. Peripheral disease with one or more tender and swollen joints, and failure of, intolerance to, or contraindication to methotrexate.

    AND

    c. Inadequate response, intolerance, or contraindication to at least THREE (3) months of treatment with NSAIDs, unless contraindicated.

6. Rheumatoid Arthritis
    a. Documented diagnosis of moderate to severe active rheumatoid arthritis; **AND**
    b. Inadequate response to at least THREE (3) months of treatment with a disease-modifying antirheumatic drug (DMARD), including **ONE** or more of the following
        i. Hydroxychloroquine
        ii. Leflunomide
        iii. Methotrexate
        iv. Sulfasalazine
        v. Tumor necrosis factor inhibitor

    AND

    c. Concurrent treatment with methotrexate, unless contraindication or intolerance.

7. Ulcerative Colitis
    a. Documented diagnosis of moderate to severe active ulcerative colitis; **AND**
    b. Intolerance or inadequate response to conventional therapy with at least **ONE** of the following:
        i. 6-mercaptopurine; or
        ii. Azathioprine; or
        iii. Oral corticosteroids; or
        iv. Salicylates.

8. Uveitis Associated with Behçet's Syndrome
    a. Loss of visual acuity or evidence of retinal involvement; **AND**
    b. Failure to respond to systemic corticosteroids or other immunosuppressants.

C. For Zymfentra (infliximab-dyyb) requests only:

Initial requests for Zymfentra may authorized when the GENERAL and CONDITION-SPECIFIC criteria AND all of the following have been met with documentation:

1. Documented diagnosis of moderate to severe or fistulizing Crohn's disease or moderate to severe ulcerative colitis**; AND**
2. Prescriber attestation or clinical documentation of **ONE** of the following:
    a. Member will complete an intravenous induction regimen with an infliximab product before using Zymfentra for subcutaneous maintenance therapy; **or**
    b. Member has been stabilized on intravenous infliximab maintenance therapy and is switching to Zymfentra for subcutaneous maintenance therapy.

II. REAUTHORIZATION / CONTINUATION OF THERAPY CRITERIA

Infliximab may be authorized for continuation of therapy when initial criteria have been met AND there is documentation of beneficial response from previous course of treatment:

A. Member continues to meet the GENERAL and CONDITION-SPECIFIC criteria in the 'Initial Therapy' section above; **AND**

B. Positive response to therapy: Stabilization or improvement in disease activity, signs and symptoms, or functional capacity as compared to baseline; **AND**

C. Absence of intolerance or adverse events from the previous course of treatment; **AND**

D. Management of Immune Checkpoint Inhibitor related Toxicity: No reauthorization. Limited to a single course of therapy and continuation of treatment may not be reauthorized.

STEP THERAPY

Step therapy criteria do not apply for members who are currently being treated with the requested medications. Step therapy is only applied for members that are new to therapy (have not received the requested drug in the last 365 days.

A. **PREFERRED PRODUCT(S): INFLECTRA (no step therapy required)**

B. NON-PREFERRED PRODUCTS may be authorized when all of the clinical criteria above are met **AND** ONE of the following:

1. Information has been provided that indicates the patient has been treated with the request medication in the past 365 days; **OR**

2. Documentation that the member has had an ineffective treatment response to the active ingredient(s) of preferred medication(s); **OR**

3. Documented intolerance, hypersensitivity, or FDA labeled contraindication to the active ingredient(s) of preferred medication(s); **OR**

4. Clinical rationale from Prescriber indicating preferred medication(s) are likely to be ineffective, likely to cause an adverse reaction or harm, or likely to be of no clinical benefit.

DOSAGE AND AUTHORIZATION TIMEFRAMES

1. Recommended Dosage:

Indication	Loading Doses	Maintenance Dose	Maximum Dose & Frequency
Rheumatoid Arthritis	3 mg/kg at weeks 0, 2, & 6	3 mg/kg every 8 weeks thereafter	Up to 10 mg/kg every 4 weeks
Ankylosing Spondylitis	5 mg/kg at weeks 0, 2, & 6	5 mg/kg every 6 weeks thereafter	5 mg/kg every 6 weeks
Crohn's Disease & Ulcerative Colitis	5 mg/kg at weeks 0, 2, & 6	5 mg/kg every 8 weeks thereafter	Up to 10 mg/kg every 8 weeks
	For Zymfentra (subcutaneous): Maintenance treatment only: 120 mg SC once every 2 weeks beginning at or after week 10 of infliximab therapy. To switch patients who are responding to maintenance therapy with an infliximab product administered IV, the first SC dose of Zymfentra should be administered in place of the next scheduled IV infusion and every two weeks thereafter.		
Psoriatic Arthritis, Plaque Psoriasis, Behçet's Uveitis	5 mg/kg at weeks 0, 2, & 6	5 mg/kg every 8 weeks thereafter	5 mg/kg every 8 weeks
Management of Immune Checkpoint Inhibitor Related Toxicity	5 mg/kg at weeks 0,2	N/A	N/A

2. Quantity: See Table above; not to exceed FDA-labeled maximum dose and frequency for indication, or as supported by CMS-approved compendia **AND** the following as applicable:

    - Zymfentra (infliximab-dyyb): 1 syringe / pen every 2 weeks

3. Authorization Period: May be authorized for up to 12 months and renewed unless otherwise specified.

    NOTE: Management of Immune Checkpoint Inhibitor related Toxicity: No reauthorization.

DRUG INFORMATION

PHARMACOLOGIC CATEGORY: Immunosuppressant Agent; Monoclonal Antibody; Tumor Necrosis Factor (TNF) Blocking Agent

PRODUCTS: Avsola; Inflectra; Remicade; Renflexis, Zymfentra

ROUTE OF ADMINISTRATION: Intravenous Infusion and Subcutaneous (Zymfentra only)

FDA-APPROVED INDICATIONS:

1. Ankylosing Spondylitis: Treatment of adults with active ankylosing spondylitis (to reduce signs/symptoms).
2. Crohn Disease: Treatment of adults and pediatric patients ≥6 years of age with moderately to severely

active Crohn disease who have had inadequate responses to conventional therapy (to reduce signs/symptoms and induce and maintain clinical remission) or to reduce the number of draining enterocutaneous and rectovaginal fistulas and maintain fistula closure in adults.
3. Plaque Psoriasis: Treatment of adults with chronic, severe (extensive and/or disabling) plaque psoriasis as an alternative to other systemic therapy.
4. Psoriatic Arthritis: Treatment of adults with psoriatic arthritis (to reduce signs/symptoms of active arthritis and inhibit progression of structural damage and improve physical function).
5. Rheumatoid Arthritis: Treatment of adults with moderately to severely active rheumatoid arthritis (with methotrexate) (to reduce signs/symptoms of active arthritis and inhibit progression of structural damage and improve physical function).
6. Ulcerative Colitis: Treatment of adults and pediatric patients ≥ 6 years of age with moderately to severely active ulcerative colitis with inadequate response to conventional therapy (to reduce signs/symptoms and induce and maintain clinical remission) or to induce/maintain mucosal healing and eliminate corticosteroid use in adults.
7. Zymfentra only: Indicated for the maintenance treatment of adults with moderately to severely active UC or CD, following treatment with an IV-administered infliximab product.

COMPENDIAL APPROVED (OFF-LABELED) USES:
Adult onset Still's disease; Hidradenitis suppurativa, severe, refractory; Juvenile idiopathic arthritis (severe), refractory to other therapies; Kawasaki disease, refractory; Multisystem inflammatory syndrome in children, refractory; associated with SARS-CoV-2 (COVID-19); Polyarteritis nodosa; Rheumatoid arthritis, monotherapy; Sarcoidosis, refractory (adjunct); Synovitis; Takayasu's disease, refractory. Uveitis; Uveitis, refractory (adjunct)

BOXED WARNING
Infliximab carries a risk of serious infections and malignancy. The risks and benefits of treatment with infliximab should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with infliximab, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy. Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with tumor necrosis factor (TNF) blockers, including infliximab. Postmarketing cases of hepatosplenic T-cell lymphoma, a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers, including infliximab. These cases have had a very aggressive disease course and have been fatal. Almost all patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with a TNF-blocker at or prior to diagnosis. The majority of reported infliximab cases have occurred in patients with Crohn disease or ulcerative colitis, and the majority were in adolescent and young adult males.

CONTRAINDICATIONS:
- Previous severe hypersensitivity (e.g., anaphylaxis, hypotension, serum sickness) to infliximab murine proteins or any component of the formulation.
- Doses >5 mg/kg in patients with moderate or severe heart failure (NYHA class III/IV).

OTHER CONSIDERATIONS:

Monitoring Parameters:
- CBC with differential (baseline); complete metabolic panel (baseline); tuberculosis (TB) screening prior to initiating and during therapy (chest Xray if TB positive); hepatitis b virus (HBV)/hepatitis C virus screening prior to initiating (all patients), HBV carriers (during and for several months following therapy); HIV screening (baseline) (AAD-NPF [Menter 2019]); LFTs (baseline and periodically during therapy; more frequently in patients with elevated LFTs; discontinue if >5 times ULN); signs/symptoms of infection, heart failure, hypersensitivity reaction, lupus-like syndrome, malignancy (eg, splenomegaly, hepatomegaly, abdominal pain, persistent fever, night sweats, weight loss). During

infusion, if reaction is noted, monitor vital signs every 2 to 10 minutes, depending on reaction severity, until normal. If a serious reaction occurs (eg, cardiovascular or cerebrovascular reaction), discontinue the infusion. Monitor improvement of symptoms and physical function assessments.

- Psoriasis patients with history of phototherapy should be monitored for nonmelanoma skin cancer. Women should be screened periodically for cervical cancer.
- The American Gastroenterological Association suggests reactive therapeutic drug monitoring to guide treatment changes in adult patients treated with infliximab for active inflammatory bowel disease (Feuerstein 2017).

CLINICAL SUMMARY / APPENDIX

Infliximab-dyyb (Inflectra) infliximab-abda (Renflexis), and infliximab-qbtx (Ixifi) are biosimilar murine-human chimeric monoclonal antibodies to infliximab (Remicade). Biosimilar denotes that the biological product is approved based on data demonstrating that it is highly similar to an FDA-approved biological product, also known as a reference product, and that there are no clinically meaningful differences between the biosimilar product and the reference product.

Avsola™ (infliximab-axxq), Inflectra™ (infliximab-dyyb), Ixifi™ (infliximab-qbtx) Renflexis™ (infliximab-abda) were approved as biosimilar to Remicade® (infliximab), indicating no clinically meaningful differences in safety and effectiveness and the same mechanism of action, route of administration, dosage form, and strength. However, minor differences in clinically inactive components are allowed. At this time, only biosimilarity has been demonstrated (not interchangeability).

Zymfentra is the first subcutaneous (SC) formulation of infliximab. Infliximab was previously only available as an IV infusion under the brand name Remicade® and its biosimilars. The product's development was based on Inflectra (infliximab-dyyb), an intravenous infliximab biosimilar referencing Remicade (infliximab). However, because the reference product does not have a subcutaneous option, Zymfentra was approved through the stand-alone biologics license application process as a novel drug; hence, Zymfentra is not a biosimilar despite its relation to Inflectra. The approval was based on data confirming Zymfentra's superior clinical effects to placebo in patients with ulcerative colitis and Crohn disease.

There is insufficient data to evaluate the concomitant use of an infliximab product with another biologic or a targeted synthetic DMARD for inflammatory conditions. Combination therapy with biologics has the potential for a higher incidence of adverse events, and controlled trial data are lacking to support additive efficacy.

REFERENCES

Government Agency

Centers for Medicare and Medicaid Services (CMS). Medicare coverage database: National coverage determination (NCD) (search: infliximab). Available from CMS. No NCD identified (LCD available but not applicable to MAC).

Prescribing Information

1. Avsola (infliximab-axxq) [prescribing information]. Thousand Oaks, CA: Amgen Inc; September 2021.
2. Inflectra (infliximab-dyyb) [prescribing information]. New York, NY: Pfizer; May 2023.
3. Remicade (infliximab) [prescribing information]. Horsham, PA: Janssen Biotech Inc; May 2020.
4. Renflexis (infliximab-abda) [prescribing information]. Whitehouse Station, NJ: Merck Sharp & Dohme Corp; January 2023.
5. Zymfentra (infliximab-dyyb) [prescribing information]. Celltrion USA Inc (per FDA), Jersey City, NJ, 2023.

Peer Reviewed Literature, Guidelines

Milliman Care Guidelines (MCG). Ambulatory Care 27th Edition ACG: A-0308 (AC). 2023.

IMPORTANT REMINDER

This Medicare Part B Step Therapy Medical Necessity Guideline is provided for informational purposes only and neither constitutes nor replaces professional medical advice. Physicians, hospitals, and other providers are expected to administer or use drugs/biologicals in the most effective and clinically appropriate manner. Treating physicians and other health care providers are solely responsible for all medical care decisions. In accordance with the member's Evidence of Coverage (EOC), every benefit plan has its own coverage provisions, limitations, and exclusions. In the event of a conflict between this policy and the member's EOC, the member's EOC provisions will take precedence.

Aspire Health Plan (AHP) adheres to Medicare guidelines, including National Coverage Determination (NCD), Local Coverage Determinations (LCDs), Local Coverage Articles (LCAs), and other relevant Medicare manuals established by CMS. Compliance with these guidelines is required when applicable. Refer to the CMS website at http://www.cms.hhs.gov. For the most up-to-date Medicare policies and coverage, please search the Medicare Coverage Database. All LCDS are the same for each state within a Jurisdiction. Medicare Part B Administrative Contractor (MAC) for CA [Jurisdiction E (1)]: Active LCDs - JE Part B – Noridian (noridianmedicare.com). In the event of a discrepancy between this policy and the Medicare NCD or LCD, the Medicare NCD/LCD will govern.

This policy is utilized by AHP to determine coverage in the absence of applicable CMS Medicare guidelines. Please refer to the links provided in the References section below to access the Medicare source materials that were used for developing this resource document. This document does not serve as a substitute for the official Medicare source materials that provide detailed information on Medicare coverage requirements. In the event of a conflict between this document and Medicare source materials, the Medicare source materials will take precedence.

The inclusion of a code in this policy does not imply that the health service it describes is covered or not covered. Benefit coverage for health services is determined by the member-specific plan document and applicable laws that may mandate coverage for a particular service. Inclusion of a code does not imply or guarantee reimbursement or payment of a claim. Other Policies and Standards may also apply. Providers are expected to retain or have access to the necessary documentation when requested in order to support coverage.

POLICY HISTORY

Version	Committee Approval Date	Summary of Changes
1	11/29/2023	New Policy
1.1	02/27/2024	Addition of Zymfentra™ SC (infliximab-dyyb)