Clinical Policy: Infliximab (Remicade), Infliximab-axxq (Avsola), Infliximab-dyyb (Inflectra, Zymfentra), and Infliximab-abda (Renflexis)

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Line of Business: Medicaid

Coding Implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Infliximab (Remicade®) and its biosimilars [infliximab-axxq (Avsola™), infliximab-dyyb (Inflectra®, Zymfentra®), and infliximab-abda (Renflexis™)] are tumor necrosis factor (TNF) blockers.

FDA Approved Indication(s)

Remicade/unbranded Remicade, Avsola, Inflectra and Renflexis are indicated for the treatment of:

- Crohn's Disease (CD):
  - Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active CD who have had an inadequate response to conventional therapy
  - Reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing CD
- Pediatric CD:
  - Reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active CD who have had an inadequate response to conventional therapy
- Ulcerative Colitis (UC):
  - Reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active UC who have had an inadequate response to conventional therapy
- Pediatric UC:
  - Reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active UC who have had an inadequate response to conventional therapy
- Rheumatoid Arthritis (RA):
  - Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active RA, in combination with methotrexate (MTX)
- Ankylosing Spondylitis (AS):
  - Reducing signs and symptoms in patients with active AS
- Psoriatic Arthritis (PsA):
  - Reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in patients with PsA

- Plaque Psoriasis (PsO):
  - Treatment of adult patients with chronic severe (i.e., extensive and/or disabling) PsO who are candidates for systemic therapy and when other systemic therapies are medically less appropriate. Infliximab should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician

Zymfentra is indicated for the treatment of:
- Moderate to severely active UC following treatment with an infliximab product administered intravenously
- Moderate to severely active CD following treatment with an infliximab product administered intravenously

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Remicade/unbranded Remicade, Avsola, Inflectra, Renflexis, and Zymfentra are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Ankylosing Spondylitis (must meet all)**:**
1. Diagnosis of AS;
2. Request is for Avsola, Inflectra, Remicade/unbranded Remicade, or Renflexis;
3. Prescribed by or in consultation with a rheumatologist;
4. Age ≥ 18 years;
5. Failure of at least TWO non-steroidal anti-inflammatory drugs (NSAIDs) at up to maximally indicated doses, each used for ≥ 4 weeks unless clinically significant adverse effects are experienced or all are contraindicated;
6. If request is for Remicade, member must use ALL of the following, unless all are contraindicated or clinically significant adverse effects are experienced (a and b):
   a. Avsola, Inflectra, and Renflexis;
   b. If member has failed Avsola, Inflectra, and Renflexis, then member must use unbranded Remicade;
7. For unbranded Remicade, member must use Avsola, Inflectra, and Renflexis, unless all are contraindicated or clinically significant adverse effects are experienced;
8. Member does not have combination use with biological disease-modifying antirheumatic drugs or Janus kinase inhibitors (*see Section III: Diagnoses/Indications for which coverage is NOT authorized*);
9. Dose does not exceed 5 mg/kg at weeks 0, 2, and 6, followed by maintenance dose of 5 mg/kg every 6 weeks (*see Appendix G for dose rounding guidelines*).

Approval duration: 6 months

B. Crohn's Disease (must meet all)**:**
1. Diagnosis of CD;
2. Prescribed by or in consultation with a gastroenterologist;

3. Member meets one of the following (a or b):
   a. Avsola, Inflectra, Remicade/unbranded Remicade, Renflexis: Age ≥ 6 years;
   b. Zymfentra: Age ≥ 18 years;
4. Member meets one of the following (a or b):
   a. Failure of a ≥ 3 consecutive month trial of at least ONE immunomodulator (e.g., azathioprine, 6-mercaptopurine [6-MP], MTX) at up to maximally indicated doses, unless clinically significant adverse effects are experienced or all are contraindicated;
   b. Medical justification supports inability to use immunomodulators (*see Appendix E*);
5. If request is for Remicade, member must use ALL of the following, unless all are contraindicated or clinically significant adverse effects are experienced (a and b):
   a. Avsola, Inflectra, and Renflexis;
   b. If member has failed Avsola, Inflectra, and Renflexis, then member must use unbranded Remicade;
6. For unbranded Remicade, member must use Avsola, Inflectra, and Renflexis, unless all are contraindicated or clinically significant adverse effects are experienced;
7. If request is for Zymfentra, provider attestation that member meets all of the following (a, b, and c, *see Appendix D*):
   a. Has received three IV induction doses of an infliximab product prior to initiation;
   b. Member is responding positively to an IV infliximab product;
   c. Member is unable to receive continued therapy with IV infliximab due to lack of caregiver or support system for assistance with administration and/or inadequate access to healthcare facility or home care interventions and/or lack of transportation to healthcare facility;
8. Member does not have combination use with biological disease-modifying antirheumatic drugs or Janus kinase inhibitors (*see Section III: Diagnoses/Indications for which coverage is NOT authorized*);
9. Dose does not exceed one of the following (a or b):
   a. Avsola, Inflectra, Remicade/unbranded Remicade, Renflexis, IV: 5 mg/kg at weeks 0, 2, and 6, followed by maintenance dose of 5 mg/kg every 8 weeks (*see Appendix G for dose rounding guidelines*);
   b. Zymfentra, SC: 120 mg every 2 weeks starting at week 10.

Approval duration: 6 months

C. Plaque Psoriasis (must meet all)**:**
1. Diagnosis of chronic-severe PsO as evidenced by involvement of one of the following (a or b):
   a. ≥ 10% of total body surface area;
   b. Hands, feet, scalp, face, or genital area;
2. Request is for Avsola, Inflectra, Remicade/unbranded Remicade, or Renflexis;
3. Prescribed by or in consultation with a dermatologist or rheumatologist;
4. Age ≥ 18 years;
5. Member meets one of the following (a, b, or c):
   a. Failure of a ≥ 3 consecutive month trial of MTX at up to maximally indicated doses;

   b. Member has intolerance or contraindication to MTX (*see Appendix D*), and failure of a ≥ 3 consecutive month trial of cyclosporine or acitretin at up to maximally indicated doses, unless clinically significant adverse effects are experienced or both are contraindicated;
   c. Member has intolerance or contraindication to MTX, cyclosporine, and acitretin, and failure of phototherapy, unless contraindicated or clinically significant adverse effects are experienced;
6. If request is for Remicade, member must use ALL of the following, unless all are contraindicated or clinically significant adverse effects are experienced (a and b):
   a. Avsola, Inflectra, and Renflexis;
   b. If member has failed Avsola, Inflectra, and Renflexis, then member must use unbranded Remicade;
7. For unbranded Remicade, member must use Avsola, Inflectra, and Renflexis, unless all are contraindicated or clinically significant adverse effects are experienced;
8. Member does not have combination use with biological disease-modifying antirheumatic drugs or Janus kinase inhibitors (*see Section III: Diagnoses/Indications for which coverage is NOT authorized*);
9. Dose does not exceed 5 mg/kg at weeks 0, 2, and 6, followed by maintenance dose of 5 mg/kg every 8 weeks (*see Appendix G for dose rounding guidelines*).

Approval duration: 6 months

D. Psoriatic Arthritis (must meet all)**:**
1. Diagnosis of PsA;
2. Request is for Avsola, Inflectra, Remicade/unbranded Remicade, or Renflexis;
3. Prescribed by or in consultation with a dermatologist or rheumatologist;
4. Age ≥ 18 years;
5. If request is for Remicade, member must use ALL of the following, unless all are contraindicated or clinically significant adverse effects are experienced (a and b):
   a. Avsola, Inflectra, and Renflexis;
   b. If member has failed Avsola, Inflectra, and Renflexis, then member must use unbranded Remicade;
6. For unbranded Remicade, member must use Avsola, Inflectra, and Renflexis, unless all are contraindicated or clinically significant adverse effects are experienced;
7. Member does not have combination use with biological disease-modifying antirheumatic drugs or Janus kinase inhibitors (*see Section III: Diagnoses/Indications for which coverage is NOT authorized*);
8. Dose does not exceed 5 mg/kg at weeks 0, 2, and 6, followed by maintenance dose of 5 mg/kg every 8 weeks (*see Appendix G for dose rounding guidelines*).

Approval duration: 6 months

E. Rheumatoid Arthritis (must meet all)**:**
1. Diagnosis of RA per American College of Rheumatology (ACR) criteria (*see Appendix H*);
2. Request is for Avsola, Inflectra, Remicade/unbranded Remicade, or Renflexis;
3. Prescribed by or in consultation with a rheumatologist;
4. Age ≥ 18 years;

5. Member meets one of the following (a or b):
   a. Failure of a ≥ 3 consecutive month trial of MTX at up to maximally indicated doses;
   b. Member has intolerance or contraindication to MTX (*see Appendix D*), and failure of a ≥ 3 consecutive month trial of at least ONE conventional disease-modifying antirheumatic drug [DMARD] (e.g., sulfasalazine, leflunomide, hydroxychloroquine) at up to maximally indicated doses, unless clinically significant adverse effects are experienced or all are contraindicated;
6. Documentation of one of the following baseline assessment scores (a or b):
   a. Clinical disease activity index (CDAI) score (*see Appendix I*);
   b. Routine assessment of patient index data 3 (RAPID3) score (*see Appendix J)*;
7. Prescribed concomitantly with MTX, or another DMARD if intolerance or contraindication to MTX;
8. If request is for Remicade, member must use ALL of the following, unless all are contraindicated or clinically significant adverse effects are experienced (a and b):
   a. Avsola, Inflectra, and Renflexis;
   b. If member has failed Avsola, Inflectra, and Renflexis, then member must use unbranded Remicade;
9. For unbranded Remicade, member must use Avsola, Inflectra, and Renflexis, unless all are contraindicated or clinically significant adverse effects are experienced;
10. Member does not have combination use with biological disease-modifying antirheumatic drugs or Janus kinase inhibitors (*see Section III: Diagnoses/Indications for which coverage is NOT authorized*);
11. Dose does not exceed 3 mg/kg at weeks 0, 2, and 6, followed by maintenance dose of 3 mg/kg every 8 weeks (*see Appendix G for dose rounding guidelines*).

Approval duration: 6 months

F. Ulcerative Colitis (must meet all)**:**

1. Diagnosis of UC;
2. Prescribed by or in consultation with a gastroenterologist;
3. Member meets one of the following (a or b):
   a. Avsola, Inflectra, Remicade/unbranded Remicade, Renflexis: Age ≥ 6 years;
   b. Zymfentra: Age ≥ 18 years;
4. Documentation of a Mayo Score ≥ 6 or modified Mayo Score ≥ 5 (*see Appendix F*);
5. Failure of an 8-week trial of systemic corticosteroids, unless contraindicated or clinically significant adverse effects are experienced;
6. If request is for Remicade, member must use ALL of the following, unless all are contraindicated or clinically significant adverse effects are experienced (a and b):
   a. Avsola, Inflectra, and Renflexis;
   b. If member has failed Avsola, Inflectra, and Renflexis, then member must use unbranded Remicade;
7. For unbranded Remicade, member must use Avsola, Inflectra, and Renflexis, unless all are contraindicated or clinically significant adverse effects are experienced;
8. If request is for Zymfentra, provider attestation that member meets all of the following (a, b, and c, *see Appendix D*):
   a. Has received three IV induction doses of an infliximab product prior to initiation;

b. Member is responding positively to an IV infliximab product;
c. Member is unable to receive continued therapy with IV infliximab due to lack of caregiver or support system for assistance with administration and/or inadequate access to healthcare facility or home care interventions and/or lack of transportation to healthcare facility;

9. Member does not have combination use with biological disease-modifying antirheumatic drugs or Janus kinase inhibitors (*see Section III: Diagnoses/Indications for which coverage is NOT authorized*);
10. Dose does not exceed one of the following (a or b):
    a. Avsola, Inflectra, Remicade/unbranded Remicade, Renflexis, IV: 5 mg/kg at weeks 0, 2, and 6, followed by maintenance dose of 5 mg/kg every 8 weeks (*see Appendix G for dose rounding guidelines*);
    b. Zymfentra, SC: 120 mg every 2 weeks starting at week 10.

Approval duration: 6 months

G. Kawasaki Disease (off-label) (must meet all)**:**
1. Diagnosis of Kawasaki disease;
2. Request is for Avsola, Inflectra, Remicade/unbranded Remicade, or Renflexis;
3. Prescribed by or in consultation with a cardiologist, allergist, immunologist, infectious disease specialist, or rheumatologist;
4. Age ≥ 6 years;
5. Failure of immune globulin (*Gammagard is preferred*), unless contraindicated or clinically significant adverse effects are experienced;
6. If request is for Remicade, member must use ALL of the following, unless all are contraindicated or clinically significant adverse effects are experienced (a and b):
    a. Avsola, Inflectra, and Renflexis;
    b. If member has failed Avsola, Inflectra, and Renflexis, then member must use unbranded Remicade;
7. For unbranded Remicade, member must use Avsola, Inflectra, and Renflexis, unless all are contraindicated or clinically significant adverse effects are experienced;
8. Member does not have combination use with biological disease-modifying antirheumatic drugs or Janus kinase inhibitors (*see Section III: Diagnoses/Indications for which coverage is NOT authorized*);
9. Dose does not exceed a single infusion of 10 mg/kg given over 2 hours (*see Appendix G for dose rounding guidelines*).

Approval duration: 4 weeks (one time approval)

H. Graft-versus-Host Disease (off-label) (must meet all)**:**
1. Diagnosis of steroid-refractory acute graft-versus-host disease (SR-aGvHD);
2. Request is for Avsola, Inflectra, Remicade/unbranded Remicade, or Renflexis;
3. Prescribed by or in consultation with an oncologist, hematologist, or bone marrow transplant specialist;
4. Used in combination with systemic corticosteroids following no response to first-line therapies (e.g., systemic corticosteroids, *see Appendix B*);

5. If request is for Remicade, member must use ALL of the following, unless all are contraindicated or clinically significant adverse effects are experienced (a and b):
   a. Avsola, Inflectra, and Renflexis;
   b. If member has failed Avsola, Inflectra, and Renflexis, then member must use unbranded Remicade;
6. For unbranded Remicade, member must use Avsola, Inflectra, and Renflexis, unless all are contraindicated or clinically significant adverse effects are experienced;
7. Member does not have combination use with biological disease-modifying antirheumatic drugs or Janus kinase inhibitors (*see Section III: Diagnoses/Indications for which coverage is NOT authorized*);
8. Request meets one of the following (a or b):
   a. Dose does not exceed 10 mg/kg/dose (IV) once weekly (*see Appendix G for dose rounding guidelines*);
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration: 1 month

I. Other diagnoses/indications (must meet all):
1. If request is for Remicade, member must use ALL of the following, unless all are contraindicated or clinically significant adverse effects are experienced (a and b):
   a. Avsola, Inflectra, and Renflexis;
   b. If member has failed Avsola, Inflectra, and Renflexis, then member must use unbranded Remicade;
2. If request is for unbranded Remicade, member must use Avsola, Inflectra, and Renflexis, unless all are contraindicated or clinically significant adverse effects are experienced;
3. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.PMN.16 for Medicaid; or
4. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 3 above does not apply, refer to the off-label use policy for the relevant line of business: CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Kawasaki Disease or Graft-versus-Host Disease (off-label):
1. Re-authorization is not permitted. Members must meet the initial approval criteria.

Approval duration: Not applicable

B. All Other Indications in Section I (must meet all)**:**
1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B)*;
2. Member meets one of the following (a or b):
   a. For RA: Member is responding positively to therapy as evidenced by one of the following (i or ii):
      i. A decrease in CDAI (*see Appendix I*) or RAPID3 (*see Appendix J*) score from baseline;
      ii. Medical justification stating inability to conduct CDAI re-assessment, and submission of RAPID3 score associated with disease severity that is similar to initial CDAI assessment or improved;
   b. For all other indications: Member is responding positively to therapy;
3. If request is for Remicade, member must use ALL of the following, unless all are contraindicated or clinically significant adverse effects are experienced (a and b):
   a. Avsola, Inflectra, and Renflexis;
   b. If member has failed Avsola, Inflectra, and Renflexis, then member must use unbranded Remicade;
4. If request is for unbranded Remicade, member must use Avsola, Inflectra, and Renflexis, unless all are contraindicated or clinically significant adverse effects are experienced;
5. Member does not have combination use with biological disease-modifying antirheumatic drugs or Janus kinase inhibitors (*see Section III: Diagnoses/Indications for which coverage is NOT authorized*);
6. If request is for a dose increase, new regimen does not exceed one of the following (*see Appendix G for dose rounding guidelines*) (a, b, c, d, or e):
   a. CD (i or ii):
      i. Avsola, Inflectra, Remicade/unbranded Remicade, Renflexis, IV (1 or 2):
         1) 5 mg/kg every 8 weeks;
         2) 10 mg/kg every 8 weeks, if age ≥ 18 years and documentation supports inadequate response to current dose;
      ii. Zymfentra, SC (both 1 and 2):
         1) Age ≥ 18 years:
         2) 120 mg every 2 weeks;
   b. UC (i or ii):
      i. Avsola, Inflectra, Remicade/unbranded Remicade, Renflexis, IV: 5 mg/kg every 8 weeks;
      ii. Zymfentra, SC (both 1 and 2):
         1) Age ≥ 18 years:
         2) 120 mg every 2 weeks;
   c. PsA, PsO: 5 mg/kg every 8 weeks;
   d. RA (i or ii):
      i. 3 mg/kg every 8 weeks;

ii. If the request is for an increase in dose or dosing frequency (*dose and frequency should not be increased simultaneously*) from the current regimen, regimen does not exceed 10 mg/kg and/or every 4 weeks, and documentation supports both of the following (1 and 2):
    1) Member has had an inadequate response to adherent use of Avsola/Remicade/unbranded Remicade/Inflectra/Renflexis concurrently with MTX or another DMARD;
    2) One of the following (a or b):
        a) Current dosing frequency is every 8 weeks: member has received at least 4 doses (14 weeks of total therapy) of Avsola/Remicade/unbranded Remicade/Inflectra/Renflexis;
        b) Current dosing frequency is < every 8 weeks: member has received at least 2 doses of Avsola/Remicade/unbranded Remicade/Inflectra/Renflexis at the current dosing frequency;

e. AS: 5 mg/kg every 6 weeks.

Approval duration: 12 months

C. Other diagnoses/indications (must meet all):
1. If request is for Remicade, member must use ALL of the following, unless all are contraindicated or clinically significant adverse effects are experienced (a and b):
    a. Avsola, Inflectra, and Renflexis;
    b. If member has failed Avsola, Inflectra, and Renflexis, then member must use unbranded Remicade;
2. If request is for unbranded Remicade, member must use Avsola, Inflectra, and Renflexis, unless all are contraindicated or clinically significant adverse effects are experienced;
3. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
    a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.PMN.255 for Medicaid; or
    b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.PMN.16 for Medicaid; or
4. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 3 above does not apply, refer to the off-label use policy for the relevant line of business: CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:
A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.PMN.53 for Medicaid or evidence of coverage documents;
B. Combination use with biological disease-modifying antirheumatic drugs (bDMARDs) or potent immunosuppressants, including but not limited to any tumor necrosis factor (TNF)

antagonists [e.g., Cimzia®, Enbrel®, Humira® and its biosimilars, Remicade® and its biosimilars, Simponi®], interleukin agents [e.g., Actemra® (IL-6RA) and its biosimilars, Arcalyst® (IL-1 blocker), Bimzelx® (IL-17A and F antagonist), Cosentyx® (IL-17A inhibitor), Ilaris® (IL-1 blocker), Ilumya™ (IL-23 inhibitor), Kevzara® (IL-6RA), Kineret® (IL-1RA), Omvoh™ (IL-23 antagonist), Siliq™ (IL-17RA), Skyrizi™ (IL-23 inhibitor), Spevigo® (IL-36 antagonist), Stelara® (IL-12/23 inhibitor) and its biosimilars, Taltz® (IL-17A inhibitor), Tremfya® (IL-23 inhibitor)], Janus kinase inhibitors (JAKi) [e.g., Cibinqo™, Olumiant™, Rinvoq™, Xeljanz®/Xeljanz® XR,], anti-CD20 monoclonal antibodies [Rituxan® and its biosimilars], selective co-stimulation modulators [Orencia®], integrin receptor antagonists [Entyvio®], tyrosine kinase 2 inhibitors [Sotyktu™], and sphingosine 1-phosphate receptor modulator [Velsipity™] because of the additive immunosuppression, increased risk of neutropenia, as well as increased risk of serious infections.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

6-MP: 6-mercaptopurine
AS: ankylosing spondylitis
CD: Crohn's disease
DMARD: disease-modifying antirheumatic drug
GI: gastrointestinal
IV: intravenous
JAKi: Janus kinase inhibitors
MTX: methotrexate
NSAID: non-steroidal anti-inflammatory drug
PsA: psoriatic arthritis
PsO: psoriasis
RA: rheumatoid arthritis
SC: subcutaneous
SR-aGvHD: steroid-refractory acute graft-versus-host disease
TNF: tumor necrosis factor
UC: ulcerative colitis

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
acitretin (Soriatane®)	**PsO** 25 or 50 mg PO QD	50 mg/day
azathioprine (Azasan®, Imuran®)	**RA** 1 mg/kg/day PO QD or divided BID **CD*** 1.5 – 2.5 mg/kg/day PO	2.5 mg/kg/day
betamethasone	**SR-aGvHD** Adults, Adolescents, and Children: 0.5 to 9 mg IM daily. Dose range is one-third to one-half the normal corticosteroid oral dose given every 12 hours	Dosage must be individualized and is highly variable depending on the nature and severity of the disease, route of

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
		treatment, and on patient response
corticosteroids	**CD*** prednisone 40 mg – 60 mg PO QD for 1 to 2 weeks, then taper daily dose by 5 mg weekly until 20 mg PO QD, and then continue with 2.5 – 5 mg decrements weekly or IV 50 – 100 mg Q6H for 1 week budesonide (Entocort EC®) 6-9 mg PO QD *Pediatric:* Prednisone 1 to 2 mg/kg/day PO QD **UC*** *Adult:* Prednisone 40 mg – 60 mg PO QD, then taper dose by 5 to 10 mg/week Budesonide (Uceris®) 9 mg PO QAM for up to 8 weeks *Pediatric:* Prednisone 1 to 2 mg/kg/day PO QD	Various
Cuprimine® (d-penicillamine)	**RA*** Initial dose: 125 or 250 mg PO QD Maintenance dose: 500 – 750 mg/day PO QD	1,500 mg/day
cyclosporine (Sandimmune®, Neoral®)	**PsO** 2.5 – 4 mg/kg/day PO divided BID **RA** 2.5 – 4 mg/kg/day PO divided BID	4 mg/kg/day
dexamethasone	**SR-aGvHD** Adults: Initially, 0.5 to 9 mg/day IV or IM, in divided doses. Children and Adolescents: 0.06 to 0.3 mg/kg/day or 1.2 to 10 mg/m²/day IM or IV in divided doses every 6 to 12 hours.	Dosage must be individualized and is highly variable depending on the nature and severity of the disease, route of treatment, and on patient response

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
hydroxychloroquine (Plaquenil®)	**RA*** Initial dose: 400 – 600 mg/day PO QD Maintenance dose: 200 – 400 mg/day PO QD	600 mg/day
leflunomide (Arava®)	**RA** Initial dose (for low risk hepatotoxicity or myelosuppression): 100 mg PO QD for 3 days Maintenance dose: 20 mg PO QD	20 mg/day
6-mercaptopurine (Purixan®)	**CD*** 50 mg PO QD or 0.75 – 1.5 mg/kg/day PO	1.5 mg/kg/day
methotrexate (Trexall®, Otrexup™, Rasuvo®, RediTrex®, Rheumatrex®)	**CD*** 15 – 25 mg/week IM or SC **PsO** 10 to 25 mg/week IM, SC or PO or 2.5 mg PO Q12 hr for 3 doses/week **RA** 7.5 mg/week PO, SC, or IM or 2.5 mg PO Q12 hr for 3 doses/week	30 mg/week
methylprednisone*	**SR-aGvHD** Adults, Adolescents, Children, and Infants: 1 to 2 mg/kg/day IV, followed by a taper.	Corticosteroid dosage must be individualized and is highly variable depending on the nature and severity of the disease, route of treatment, and on patient response
NSAIDs (e.g., indomethacin, ibuprofen, naproxen, celecoxib)	**AS** Varies	Varies
Pentasa® (mesalamine)	**CD, UC** 1,000 mg PO QID	4 g/day
prednisone	**SR-aGvHD** Varies	Varies
Ridaura® (auranofin)	**RA** 6 mg PO QD or 3 mg PO BID	9 mg/day (3 mg TID)

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
sulfasalazine (Azulfidine®)	**RA** Initial dose: 500 mg to 1,000 mg PO QD for the first week. Increase the daily dose by 500 mg each week up to a maintenance dose of 2 g/day. Maintenance dose: 2 g/day PO in divided doses	RA: 3 g/day UC: 4 g/day
tacrolimus (Prograf®)	**CD*** 0.27 mg/kg/day PO in divided doses or 0.15 – 0.29 mg/kg/day PO **PsO** 0.05 – 0.15 mg/kg/day PO	N/A
Immune globulin (e.g., Gammagard®)	**Kawasaki disease** Varies based on formulation	Varies based on formulation

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.
**Off-label*

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s):
  - Doses > 5 mg/kg in patients with moderate-to-severe heart failure (*Avsola, Inflectra, Remicade, and Renflexis only*)
  - Known hypersensitivity to inactive components of the product or to any murine proteins
- Boxed warning(s):
  - Serious infections
  - Malignancy

Appendix D: General Information

- Definition of failure of MTX or DMARDs
  - Child-bearing age is not considered a contraindication for use of MTX. Each drug has risks in pregnancy. An educated patient and family planning would allow use of MTX in patients who have no intention of immediate pregnancy.
  - Social use of alcohol is not considered a contraindication for use of MTX. MTX may only be contraindicated if patients choose to drink over 14 units of alcohol per week. However, excessive alcohol drinking can lead to worsening of the condition, so patients who are serious about clinical response to therapy should refrain from excessive alcohol consumption.
- Examples of positive response to therapy may include, but are not limited to:
  - Reduction in joint pain/swelling/tenderness
  - Improvement in ESR/CRP levels

    - Improvements in activities of daily living
- Infliximab used in the treatment of unspecified iridocyclitis (anterior uveitis) has primarily been evaluated in case reports and uncontrolled case series. One phase II clinical trial by Suhler and associates (2009) reported the 2-year follow-up data of patients with refractory uveitis treated with intravenous infliximab as part of a prospective clinical trial. Their 1-year data, published in 2005 (Suhler, 2005) reported reasonable initial success, but an unexpectedly high incidence of adverse events. Of their 23 patients, 7 developed serious adverse events, including 3 thromboses, 1 malignancy, 1 new onset of congestive heart failure, and 2 cases of drug-induced lupus. The American Optometric Association anterior uveitis clinical practice guidelines recommend alternative therapies that include ophthalmic corticosteroids (e.g., prednisolone, dexamethasone, fluoromethalone) and anticholinergics (e.g., atropine, cyclopentolate, homatropine). If the disease has not responded to topical therapy, oral corticosteroids can be considered.
- Zymfentra is indicated as maintenance treatment only, starting at week 10 and thereafter. All patients must complete an intravenous induction regimen with an infliximab product before starting Zymfentra. To switch patients who are responding to maintenance therapy with an infliximab product administered intravenously, administer the first subcutaneous dose of Zymfentra in place of the next scheduled intravenous infusion and every two weeks thereafter.

Appendix E: Immunomodulator Medical Justification

- The following may be considered for medical justification supporting inability to use an immunomodulator for Crohn's disease:
    - Inability to induce short-term symptomatic remission with a 3-month trial of systemic glucocorticoids
    - High-risk factors for intestinal complications may include:
        - Initial extensive ileal, ileocolonic, or proximal GI involvement
        - Initial extensive perianal/severe rectal disease
        - Fistulizing disease (e.g., perianal, enterocutaneous, and rectovaginal fistulas)
        - Deep ulcerations
        - Penetrating, stricturing or stenosis disease and/or phenotype
        - Intestinal obstruction or abscess
    - High risk factors for postoperative recurrence may include:
        - Less than 10 years duration between time of diagnosis and surgery
        - Disease location in the ileum and colon
        - Perianal fistula
        - Prior history of surgical resection
        - Use of corticosteroids prior to surgery

Appendix F: Mayo Score or Modified Mayo Score

- Mayo Score: evaluates ulcerative colitis stage, based on four parameters: stool frequency, rectal bleeding, endoscopic evaluation and Physician's global assessment. Each parameter of the score ranges from zero (normal or inactive disease) to 3 (severe activity) with an overall score of 12.

Score	Decoding
0 – 2	Remission
3 – 5	Mild activity
6 – 10	Moderate activity
>10	Severe activity

- Modified Mayo Score: developed from the full Mayo score and evaluates ulcerative colitis stage, based on three parameters: stool frequency, rectal bleeding, and endoscopic evaluation. The modified Mayo Score gives a maximum overall score of 9. The FDA currently accepts the modified Mayo Score for the assessment of disease activity in pivotal UC clinical trials.

Appendix G: Dose Rounding Guidelines

Weight-based Dose Range	Vial Quantity Recommendation
≤ 104.99 mg	1 vial of 100 mg/20 mL
105 to 209.99 mg	2 vials of 100 mg/20 mL
210 to 314.99 mg	3 vials of 100 mg/20 mL
315 to 419.99 mg	4 vials of 100 mg/20 mL
420 to 524.99 mg	5 vials of 100 mg/20 mL
525 to 629.99 mg	6 vials of 100 mg/20 mL
630 to 734.99 mg	7 vials of 100 mg/20 mL
735 to 839.99 mg	8 vials of 100 mg/20 mL

Appendix H: The 2010 ACR Classification Criteria for RA

Add score of categories A through D; a score of ≥ 6 out of 10 is needed for classification of a patient as having definite RA.

A	**Joint involvement**	Score
	1 large joint	0
	2-10 large joints	1
	1-3 small joints (with or without involvement of large joints)	2
	4-10 small joints (with or without involvement of large joints)	3
	> 10 joints (at least one small joint)	5
B	**Serology (at least one test result is needed for classification)**	
	Negative rheumatoid factor (RF) *and* negative anti-citrullinated protein antibody (ACPA)	0
	Low positive RF *or* low positive ACPA * *Low: < 3 x upper limit of normal*	2
	High positive RF *or* high positive ACPA * *High: ≥ 3 x upper limit of normal*	3
C	**Acute phase reactants (at least one test result is needed for classification)**	
	Normal C-reactive protein (CRP) and normal erythrocyte sedimentation rate (ESR)	0
	Abnormal CRP or abnormal ESR	1
D	**Duration of symptoms**	
	< 6 weeks	0
	≥ 6 weeks	1

Appendix I: Clinical Disease Activity Index (CDAI) Score
The Clinical Disease Activity Index (CDAI) is a composite index for assessing disease activity in RA. CDAI is based on the simple summation of the count of swollen/tender joint count of 28 joints along with patient and physician global assessment on VAS (0–10 cm) Scale for estimating disease activity. The CDAI score ranges from 0 to 76.

CDAI Score	Disease state interpretation
≤ 2.8	Remission
> 2.8 to ≤ 10	Low disease activity
> 10 to ≤ 22	Moderate disease activity
> 22	High disease activity

Appendix J: Routine Assessment of Patient Index Data 3 (RAPID3) Score
The Routine Assessment of Patient Index Data 3 (RAPID3) is a pooled index of the three patient-reported ACR core data set measures: function, pain, and patient global estimate of status. Each of the individual measures is scored 0 – 10, and the maximum achievable score is 30.

RAPID3 Score	Disease state interpretation
≤ 3	Remission
3.1 to 6	Low disease activity
6.1 to 12	Moderate disease activity
> 12	High disease activity

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
CD, UC	Initial dose: **Avsola, Inflectra, Remicade, Renflexis:** *Adults/Pediatrics:* 5 mg/kg IV at weeks 0, 2 and 6 Maintenance dose: **Avsola, Inflectra, Remicade, Renflexis:** *Adults/Pediatrics:* 5 mg/kg IV every 8 weeks. For CD: Some adult patients who initially respond to treatment may benefit from increasing the dose to 10 mg/kg if they later lose their response. **Zymfentra:** *Adults:* 120 mg SC every 2 weeks starting at week 10	CD, Adults: 10 mg/kg IV every 8 weeks or 120 mg SC every 2 weeks UC, Adults: 5 mg/kg IV every 8 weeks or 120 mg SC every 2 weeks Pediatrics: 5 mg/kg IV every 8 weeks
PsA PsO	Initial dose: 5 mg/kg IV at weeks 0, 2 and 6 Maintenance dose: 5 mg/kg IV every 8 weeks	5 mg/kg every 8 weeks
RA	In conjunction with MTX	10 mg/kg every 4 weeks

Indication	Dosing Regimen	Maximum Dose
	Initial dose: 3 mg/kg IV at weeks 0, 2 and 6 Maintenance dose: 3 mg/kg IV every 8 weeks Some patients may benefit from increasing the dose up to 10 mg/kg or treating as often as every 4 weeks.	
AS	Initial dose: 5 mg/kg IV at weeks 0, 2 and 6 Maintenance dose: 5 mg/kg IV every 6 weeks	5 mg/kg every 6 weeks

VI. Product Availability

Drug Name	Availability
Infliximab (Remicade)	Single-use vial: 100 mg/20 mL
Infliximab-axxq (Avsola)	Single-dose vial: 100 mg/20 mL
Infliximab-dyyb (Inflectra)	Single-use vial: 100 mg/20 mL
Infliximab-dyyb (Zymfentra)	• Single-dose prefilled syringe: 120 mg/mL • Single-dose prefilled syringe with needle shield: 120 mg/mL • Single-dose prefilled pen: 120 mg/mL
Infliximab-abda (Renflexis)	Single-use vial: 100 mg/20 mL

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Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J1745	Injection, infliximab, excludes biosimilar, 10 mg
J1748	Injection, infliximab-dyyb (zymfentra), 10 mg
Q5103	Injection, infliximab-dyyb, biosimilar, (inflectra), 10 mg
Q5104	Injection, infliximab-abda, biosimilar, (renflexis), 10 mg
Q5121	Injection, infliximab-axxq, biosimilar, (avsola), 10 mg
S9359	Home infusion therapy, anti-tumor necrosis factor intravenous therapy; (e.g., Infliximab); administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem

Reviews, Revisions, and Approvals	Date	P&T Approval Date
2Q 2021 annual review: added additional criteria related to diagnosis of chronic severe PsO per 2019 AAD/NPF guidelines specifying at least 10% BSA involvement or involvement of areas that severely impact daily function; added redirection to preferred biosimilars to other diagnoses/indications; added combination of bDMARDs under Section III; updated CDAI table with ">" to prevent overlap in classification of severity; references reviewed and updated.	02.23.21	05.21
Per June SDC and prior clinical guidance, added Avsola to list of biosimilar infliximab products that must be used prior to Remicade; added HCPCS code for Avsola.	06.02.21	08.21
2Q 2022 annual review: for PsO, allowed phototherapy as alternative to systemic conventional DMARD if contraindicated or clinically significant adverse effects are experienced; added off-label use for Kawasaki disease; removed unspecified iridocyclitis (ICD10 H20.9) from Section III; applied legacy Wellcare Medicaid (WCG.CP.PHAR.254 to be retired); revised redirection language to biosimilars to "must use" to clarify intent; reiterated requirement against combination use with a bDMARD or JAKi from Section III to Sections I and II; references reviewed and updated.	02.19.22	05.22
2Q 2023 annual review: no significant changes; template changes applied to other diagnoses/indications and continued therapy section; references reviewed and updated.	02.08.23	05.23
RT4: added newly approved Zymfentra to criteria; for AS, PsO, PsA, RA, Kawasaki Disease, added "request is for Avsola, Inflectra, Remicade, or Renflexis" to initial approval criteria; added Tofidence and Zymfentra to section III.B.	11.09.23	02.24
2Q 2024 annual review: for Renflexis, removed "re-administration to patients who have experienced severe hypersensitivity reaction to infliximab products" in contraindications section; added Bimzelx, Omvoh, Sotyktu, Wezlana, and Velsipity to section III.B; references reviewed and updated.	01.31.24	05.24
Added HCPCS code [J1748].	06.03.24	
Per June SDC: modified Remicade redirection by adding if member has failed Avsola, Inflectra, and Renflexis, member must use unbranded Remicade; for unbranded Remicade, added redirection to Avsola, Inflectra, and Renflexis; for CD and UC, added additional requirement for Zymfentra requests requiring provider attestation that "member is unable to receive continued therapy with IV infliximab due to lack of caregiver or support system for assistance with administration and/or inadequate access to healthcare facility or home care interventions and/or lack of transportation to healthcare facility."	06.06.24	08.24

Reviews, Revisions, and Approvals	Date	P&T Approval Date
2Q 2025 annual review: for UC initial criteria, added option for documentation of modified Mayo Score ≥ 5; for Appendix F, added supplemental information on modified Mayo Score; for Kawasaki disease, updated maximum dose from 5 mg/kg given over 2 hours to 10 mg/kg given over 2 hours; for continued therapy section, removed "if new dosing regimen, approve for 6 months" for approval duration; updated section III.B with Spevigo and biosimilar verbiage; references reviewed and updated. Added off-label criteria for steroid-refractory acute graft-versus-host disease as supported by NCCN compendium.	03.27.25	05.25

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible

for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members, and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.