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

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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®) and infliximab-abda (Renflexis®)], are tumor necrosis factor (TNF) blockers.

FDA Approved Indication(s)

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 disease
- 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.

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.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Remicade, Avsola, Inflectra, and Renflexis are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Ankylosing Spondylitis (must meet all)**:**

1. Diagnosis of AS;
2. Prescribed by or in consultation with a rheumatologist;
3. Age ≥ 18 years;
4. Failure of at least TWO non-steroidal anti-inflammatory drugs (NSAIDs) at up to maximally indicated doses, each used for ≥ 4 weeks unless contraindicated or clinically significant adverse effects are experienced;
5. If request is for Avsola, Inflectra or Renflexis, member meets both of the following (a and b):
   a. Member has experienced clinically significant adverse effects to Remicade or has contraindication(s) to its excipients;
   b. Failure of 2 of the following, each used for ≥ 3 consecutive months unless clinically significant adverse effects are experienced or all are contraindicated: etanercept *(Enbrel is preferred*), adalimumab *(Humira is preferred),* Cosentyx®, golimumab (*Simponi Aria is preferred*);
      **Prior authorization may be required for etanercept, adalimumab, Cosentyx, and golimumab*
6. 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. Age ≥ 6 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], methotrexate [MTX]) at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
   b. Medical justification supports inability to use immunomodulators (*see Appendix E*);
5. If request is for Avsola, Inflectra or Renflexis, member meets both of the following (a and b):
   a. Member has experienced clinically significant adverse effects to Remicade or has contraindication(s) to its excipients;
   b. Failure of adalimumab (*Humira® is preferred*) AND subcutaneous Stelara®, each used for ≥ 3 consecutive months, unless clinically significant adverse effects are experienced or both are contraindicated;
      **Prior authorization may be required for adalimumab and Stelara*
6. 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

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. Prescribed by or in consultation with a dermatologist or rheumatologist;
3. Age ≥ 18 years;
4. 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 cyclosporine or acitretin at up to maximally indicated doses, unless clinically significant adverse effects are experienced or both are contraindicated;

5. If request is for Avsola, Inflectra or Renflexis, member meets both of the following (a and b):
   a. Member has experienced clinically significant adverse effects to Remicade or has a contraindication(s) to its excipients;
   b. Failure of 2 of the following, each used for ≥ 3 consecutive months unless clinically significant adverse effects are experienced or all are contraindicated: adalimumab (*Humira is preferred*), Cosentyx, subcutaneous Stelara, Skyrizi®, Tremfya®;
      **Prior authorization may be required for adalimumab, Cosentyx, Stelara, Skyrizi, and Tremfya*
6. 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. Prescribed by or in consultation with a dermatologist or rheumatologist;
3. Age ≥ 18 years;
4. If request is for Avsola, Inflectra or Renflexis, member meets both of the following (a and b):
   a. Member has experienced clinically significant adverse effects to Remicade or has contraindication(s) to its excipients;
   b. Failure of 2 of the following, each used for ≥ 3 consecutive months, unless clinically significant adverse effects are experienced or all are contraindicated: Cosentyx, etanercept (*Enbrel is preferred*), adalimumab (*Humira is preferred*), Otezla®, golimumab (*Simponi Aria is preferred*), subcutaneous Stelara, Xeljanz, Xeljanz XR;
      **Prior authorization may be required for Cosentyx, etanercept, adalimumab, Otezla, golimumab, Stelara, Xeljanz, Xeljanz XR*
5. 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. Prescribed by or in consultation with a rheumatologist;
3. Age ≥ 18 years;
4. 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;
5. 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 (RAPID) score (*see Appendix J*);
6. If request is for Avsola, Inflectra or Renflexis, member meets both of the following (a and b):
   a. Member has experienced clinically significant adverse effects to Remicade or has contraindication(s) to its excipients;
   b. Failure of 2 of the following, each used for ≥ 3 consecutive months unless clinically significant adverse effects are experienced or all are contraindicated: etanercept *(Enbrel® is preferred*), adalimumab *(Humira is preferred),* Rinvoq®, Xeljanz®, Xeljanz XR®, golimumab (*Simponi Aria® is preferred*);
      **Prior authorization may be required for etanercept, adalimumab, Rinvoq, Xeljanz, Xeljanz XR, and golimumab*
7. Prescribed concomitantly with MTX, or another DMARD if intolerance or contraindication to MTX;
8. 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. Age ≥ 6 years;
4. Documentation of Mayo Score ≥ 6 (*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 Avsola, Inflectra or Renflexis, member meets both of the following (a and b):
   a. Member has experienced clinically significant adverse effects to Remicade or has contraindication(s) to its excipients;
   b. If age ≥ 18 years: Failure of a ≥ 3 consecutive month trial of TWO of the following, unless clinically significant adverse effects are experienced or all are contraindicated: adalimumab (*Humira is preferred*), subcutaneous Stelara, Xeljanz®, Xeljanz XR®;
   **Prior authorization may be required for adalimumab, Stelara, Xeljanz, and Xeljanz XR*
7. Dose does not exceed 5 mg/kg at weeks 0, 2, and 6, followed by maintenance dose of 5 mg/kg then every 8 weeks (*see Appendix G for dose rounding guidelines*).

Approval duration: 6 months

G. Other diagnoses/indications
1. If request is for Avsola, Inflectra, or Renflexis, member has experienced clinically significant adverse effects to Remicade or has contraindication(s) to its excipients);
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. All Indications in Section I (must meet all)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
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 ability 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 a dose increase, new regimen does not exceed one of the following (*see Appendix G for dose rounding guidelines*) (a, b, c, or d):
   a. CD (i or ii):
      i. 5 mg/kg every 8 weeks;
      ii. 10 mg/kg every 8 weeks, if age ≥ 18 years and documentation supports inadequate response to current dose;
   b. UC, PsA, PsO: 5 mg/kg every 8 weeks;
   c. RA (i or ii):
      i. 3 mg/kg every 8 weeks;
      ii. If the request is for an increase in dose or dosing frequency (*only 1 may be increased at a time*) from the current regimen, regimen does not exceed 10 mg/kg and/or every 4 weeks, and documentation supports both of the following (a and b):
         a) Member has had an inadequate response to adherent use of Remicade/Avsola/Inflectra/Renflexis concurrently with MTX or another DMARD;
         b) One of the following (1 or 2):
            1) Current dosing frequency is every 8 weeks: Member has received at least 4 doses (14 weeks of total therapy) of Remicade/Avsola/Inflectra/Renflexis;

2) Current dosing frequency is < every 8 weeks: Member has received at least 2 doses of Remicade/Avsola/Inflectra/Renflexis at the current dosing frequency;

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

Approval duration: 12 months (*If new dosing regimen, approve for 6 months*)

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. If request is for Avsola, Inflectra, or Renflexis: Member has experienced clinically significant adverse effects to Remicade or has contraindication(s) to its excipients;
2. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
3. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

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 policy – ERX.PA.01 or evidence of coverage documents;

B. Unspecified iridocyclitis (ICD10 H20.9);

C. Combination use of biological disease-modifying antirheumatic drugs (bDMARDs), including any tumor necrosis factor (TNF) antagonists [Cimzia®, Enbrel®, Simponi®, Avsola™, Inflectra™, Remicade®, Renflexis™], interleukin agents [Arcalyst® (IL-1 blocker), Ilaris® (IL-1 blocker), Kineret® (IL-1RA), Actemra® (IL-6RA), Kevzara® (IL-6RA), Stelara® (IL-12/23 inhibitor), Cosentyx® (IL-17A inhibitor), Taltz® (IL-17A inhibitor), Siliq™ (IL-17RA), Ilumya™ (IL-23 inhibitor), Skyrizi™ (IL-23 inhibitor), Tremfya® (IL-23 inhibitor)], janus kinase inhibitors (JAKi) [Xeljanz®/Xeljanz® XR, Rinvoq™], anti-CD20 monoclonal antibodies [Rituxan®, Riabni™, Ruxience™, Truxima®, and Rituxan Hycela®], selective co-stimulation modulators [Orencia®], or integrin receptor antagonists [Entyvio®] because of the possibility of increased immunosuppression, neutropenia and increased risk of infection.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

6-MP: 6-mercaptopurine
AS: ankylosing spondylitis
CD: Crohn's disease
CDAI: clinical disease activity index
DMARD: disease-modifying antirheumatic drug
MTX: methotrexate
NSAID: non-steroidal anti-inflammatory drug
PsA: psoriatic arthritis
PsO: psoriasis
RA: rheumatoid arthritis
RAPID3: routine assessment of patient index data 3
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 PO QD or divided BID **CD*, UC*** 1.5 – 2 mg/kg/day PO	2.5 mg/kg/day
corticosteroids	**CD***	Various

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	prednisone 40 mg PO QD for 2 weeks or IV 50 – 100 mg Q6H for 1 week budesonide (Entocort EC®) 6 – 9 mg PO QD	
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
hydroxychloroquine (Plaquenil®)	**RA*** Initial dose: 400 – 600 mg PO QD Maintenance dose: 200 – 400 mg PO QD	600 mg/day
leflunomide (Arava®)	**RA** 100 mg PO QD for 3 days, then 20 mg PO QD	20 mg/day
6-mercaptopurine (Purixan®)	**CD*, UC*** 50 mg PO QD or 1 – 2 mg/kg/day PO	2 mg/kg/day
methotrexate (Rheumatrex®)	**CD*, UC*** 15 – 25 mg/week IM or SC **PsO** 10 – 25 mg/week 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
NSAIDs (e.g., indomethacin, ibuprofen, naproxen, celecoxib)	**AS** Varies	Varies
Pentasa® (mesalamine)	**CD, UC** 1,000 mg PO QID	4 g/day
Ridaura® (auranofin)	**RA** 6 mg PO QD or 3 mg PO BID	9 mg/day (3 mg TID)
sulfasalazine (Azulfidine®)	**RA** 2 g/day PO in divided doses **UC** Initial dose: *Adults*: 3 – 4 g/day PO in divided doses (not to exceed Q8 hrs) *Pediatrics*: 40 – 60 mg/kg/day PO in 3 – 6 divided doses Maintenance dose:	RA: 3 g/day UC: 4 g/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	Adults: 2 g PO daily *Pediatrics*: 30 mg/kg/day PO in 4 divided doses	
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
Cosentyx® (secukinumab)	**AS** With loading dose: 150 mg at weeks 0, 1, 2, 3, and 4, followed by 150 mg every 4 weeks Without loading dose: 150 mg every 4 weeks **PsA** With loading dose: 150 mg SC at week 0, 1, 2, 3, and 4, followed by 150 mg every 4 weeks Without loading dose: 150 mg SC every 4 weeks If a patient continues to have active psoriatic arthritis, consider a dosage of 300 mg. **PsO (with or without PsA)** 300 mg SC at week 0, 1, 2, 3, and 4, followed by 300 mg every 4 weeks	AS: 150 mg every 4 weeks PsA, PsO: 300 mg every 4 weeks
Enbrel® (etanercept)	**AS** 50 mg SC once weekly **PsA, RA** 25 mg SC twice weekly or 50 mg SC once weekly	50 mg/week
Humira® (adalimumab)	**AS** 40 mg SC every other week **CD** <u>Initial dose:</u> *Adults:* 160 mg SC on Day 1, then 80 mg SC on Day 15 *Pediatrics:* Weight 17 kg (37 lbs) to < 40 kg (88 lbs): 80 mg SC on Day 1, then 40 mg SC on Day 15 Weight ≥ 40 kg (88 lbs): 160 mg SC on Day 1, then 80 mg SC on Day 15 <u>Maintenance dose:</u> *Adults:* 40 mg SC every other week starting on Day 29	AS, CD, PsO, PsA, UC: 40 mg every other week RA: 40 mg/week

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	Pediatrics: Weight 17 kg (37 lbs) to < 40 kg (88 lbs): 20 mg SC every other week starting on Day 29 Weight ≥ 40 kg (88 lbs): 40 mg SC every other week starting on Day 29 **PsO** Initial dose: 80 mg SC Maintenance dose: 40 mg SC every other week starting one week after initial dose **PsA** 40 mg SC every other week **RA** 40 mg SC every other week (may increase to once weekly) **UC** Initial dose: 160 mg SC on Day 1, then 80 mg SC on Day 15 Maintenance dose: 40 mg SC every other week starting on Day 29	
Otezla® (apremilast)	**PsA** Initial dose: Day 1: 10 mg PO QAM Day 2: 10 mg PO QAM and 10 mg PO QPM Day 3: 10 mg PO QAM and 20 mg PO QPM Day 4: 20 mg PO QAM and 20 mg PO QPM Day 5: 20 mg PO QAM and 30 mg PO QPM Maintenance dose: Day 6 and thereafter: 30 mg PO BID	60 mg/day
Rinvoq® (upadacitnib)	**RA** 15 mg PO QD	15 mg/day
Simponi Aria® (golimumab)	**AS, PsA, RA** Initial dose: 2 mg/kg IV at weeks 0 and 4 Maintenance dose: 2 mg/kg IV every 8 weeks	2 mg/kg every 8 weeks
Skyrizi® (risankizumab-rzaa)	**PsO** 150 mg (two 75 mg injections) SC at Week 0, Week 4 and every 12 weeks thereafter	150 mg every 12 weeks
Stelara® (ustekinumab)	**CD**	CD: 90 mg every 8 weeks

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	Weight based dosing IV at initial dose, followed by 90 mg SC every 8 weeks Weight ≤ 55 kg: 260 mg Weight 55 kg to 85 kg: 390 mg Weight > 85 kg: 520 mg **PsA** 45 mg SC at weeks 0 and 4, followed by 45 mg every 12 weeks **PsO** Weight based dosing SC at weeks 0 and 4, followed by maintenance dose every 12 weeks *Adult:* Weight ≤ 100 kg: 45 mg Weight > 100 kg: 90 mg *Pediatrics (Age 12 years and older):* Weight < 60 kg: 0.75 mg/kg Weight 60 to 100 kg: 45 mg Weight > 100kg: 90 mg **UC** Weight based dosing IV at initial dose, followed by 90 mg SC every 8 weeks Weight ≤ 55 kg: 260 mg Weight 55 kg to 85 kg: 390 mg Weight > 85 kg: 520 mg	PsA: 45 mg every 12 weeks PsO: 90 mg every 12 weeks UC: 90 mg every 8 weeks
Tremfya® (guselkumab)	**PsO** Initial dose: 100 mg SC at weeks 0 and 4 Maintenance dose: 100 mg SC every 8 weeks	100 mg every 8 weeks
Xeljanz® (tofacitinib, immediate-release)	**PsA, RA** 5 mg PO BID **UC** 10 mg PO BID for 8 weeks; then 5 mg PO BID	PsA, RA: 10 mg/day UC, maintenance: 10 mg/day
Xeljanz XR® (tofacitinib, extended-release)	**PsA, RA** 11 mg PO QD **UC** 22 mg PO QD for 8 weeks; then 11 mg PO QD	PsA, RA: 11 mg/day UC, maintenance: 11 mg/day

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
  - Re-administration to patients who have experienced a severe hypersensitivity reaction to infliximab products
  - 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.

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

- 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

- The following may be considered for medical justification supporting inability to use an immunomodulator for ulcerative colitis:
  - Documentation of Mayo Score 6 – 12 indicative of moderate to severe ulcerative colitis.

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

CDAI Score	Disease state interpretation
> 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: *Adults/Pediatrics:* 5 mg/kg IV at weeks 0, 2 and 6 Maintenance dose: *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	CD, Adults: 10 mg/kg every 8 weeks UC, Adults: 5 mg/kg every 8 weeks Pediatrics: 5 mg/kg 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 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	10 mg/kg 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-use vial: 100 mg/20 mL
Infliximab-dyyb (Inflectra)	Single-use vial: 100 mg/20 mL
Infliximab-abda (Renflexis)	Single-use vial: 100 mg/20 mL

VII. References

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Reviews, Revisions, and Approvals	Date	P&T Approval Date
Added newly approved biosimilar Renflexis to the policy.	06.17	08.17
4Q17 Annual Review Aligned diagnostic criteria per 3Q17 TCRs: AS: added specialist requirement CD: modified diagnostic criteria from requirement of poor prognostic factors to appropriate diagnosis only from specialist, added trial duration of 3 months for thiopurine or MTX CD, UC: removed "active" verbiage;	10.02.17	11.17

Reviews, Revisions, and Approvals	Date	P&T Approval Date
PsA: listed alternatives for those not a candidate for MTX (leflunomide, sulfasalazine, or cyclosporine); PsO: diagnostic criteria modified to require verifiable information and removed BSA and involvement of specific areas; removed requirement of topical tx since systemic tx is already required; RA: removed requirement for submission of diagnostic lab since a specialist is required to prescribe or be consulted UC: clarified preferencing for Humira for adults only. Removed UpToDate references. Specified max weight-based dose and frequency.		
2Q 2018 annual review: modified gastroenterologist specialty requirement to gastrointestinal specialist for CD/UC; added aminosalicylate as an option for trial and failure for UC; modified trial and failure for RA to at least one conventional DMARD; added preferencing for infliximab products for all indications; references reviewed and updated.	02.27.18	05.18
4Q 2018 annual review: modified prescriber specialist from GI specialist to gastroenterologist for CD and UC; added trial and failure of immunosuppressants, or medical necessity for use of biologics in CD; allowed bypassing conventional DMARDs for axial PsA and required trial of NSAIDs; references reviewed and updated.	09.04.18	11.18
2Q 2019 annual review: removed trial and failure requirement of conventional DMARDs (e.g., MTX)/NSAIDs for biologic DMARDs for PsA per ACR/NPF 2018 guidelines; revised requirement of trial and failure of biologics to preferred TNF inhibitors and Otezla for PsA per ACR/NPF 2018 guidelines; added Xeljanz/Xeljanz XR to list of trial options for RA; references reviewed and updated.	03.05.19	05.19
RT4: updated FDA-approved language to indicate Inflectra and Renflexis are approved for use in pediatric ulcerative colitis; revised age 18 years requirement to apply only to Humira redirection.	07.09.19	
Added unspecified iridocyclitis to Section III as an excluded use for Inflectra, Remicade, and Renflexis.	01.14.19	02.20
2Q 2020 annual review: added Avsola to the policy; for RA, added specific diagnostic criteria for definite RA, baseline CDAI score requirement, and decrease in CDAI score as positive response to therapy, for UC, revised redirection from AZA, 6-MP, ASA to systemic corticosteroids, and added requirement for Mayo score of at least 6; added dose rounding guidelines for all indications, added Stelara, Xeljanz, and Xeljanz XR as preferred options for redirection per formulary status; for RA, added Rinvoq as a preferred option for redirection per formulary status; for PsO, added Tremfya as a preferred option for redirection per formulary status; references reviewed and updated.	02.29.20	05.20
Revised typo in Appendix E from “normal ESR” to “abnormal ESR” for a point gained for ACR Classification Criteria.	11.22.20	
Added criteria for RAPID3 assessment for RA given limited in-person visits during COVID-19 pandemic, updated appendices.	11.24.20	02.21
Per CVS, removed redirection to Kevzara for RA despite preferred status on Formulary 500/550 files in order to maximize rebates	02.01.21	
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; redirect Avsola to Remicade (preferred) for all indications and applied redirection to preferred biosimilar to other diagnoses/indications; added Skyrizi as a preferred option for PsO per formulary status; added combination of	02.23.21	05.21

Reviews, Revisions, and Approvals	Date	P&T Approval Date
bDMARDs under Section III; updated CDAI table with ">" to prevent overlap in classification of severity; references reviewed and updated.		

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.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. 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.