Clinical Policy: Infliximab (Remicade, Inflectra, Renflexis)

Reference Number: HIM.PA.SP58
Effective Date: 02.27.18
Last Review Date: 05.18 Coding Implications
Line of Business: Health Insurance Marketplace Revision Log

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

Description

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

FDA Approved Indication(s)

Remicade, Inflectra* and Renflexis* is 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.

Renflexis and Inflectra are approved for all of the above indications except for pediatric UC.

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, Inflectra, and Renflexis are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Crohn's Disease (must meet all)**:**

1. Diagnosis of CD;
2. Prescribed by or in consultation with a gastrointestinal (GI) specialist;
3. Age ≥ 6 years;
4. 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 contraindicated or clinically significant adverse effects are experienced;
5. Failure of a ≥ 3 consecutive month trial of adalimumab *(Humira® is preferred)* unless contraindicated or clinically significant adverse effects are experienced;
   **Prior authorization is required for adalimumab*
6. If request is for Remicade, member has experienced clinically significant adverse effects or has a contraindication to excipients from Inflectra and Renflexis;
7. Dose does not exceed 5 mg/kg at weeks 0, 2, and 6, followed by maintenance dose of 5 mg/kg every 8 weeks.

Approval duration: 6 months

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

1. Diagnosis of UC;
2. Prescribed by or in consultation with a GI specialist;
3. Age ≥ 6 years;
4. Failure of a ≥ 3 consecutive month trial of azathioprine, 6-MP, or an aminosalicylate (e.g., sulfasalazine) at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
5. If age ≥ 18 years, failure of a ≥ 3 consecutive month trial of adalimumab (*Humira is preferred*), unless contraindicated or clinically significant adverse effects are experienced;
   **Prior authorization is required for adalimumab*
6. If age is ≥ 18 years and request is for Remicade, member has experienced clinically significant adverse effects or has a contraindication to excipients from Inflectra and Renflexis;
7. Dose does not exceed 5 mg/kg at weeks 0, 2, and 6, followed by maintenance dose of 5 mg/kg every 8 weeks.

Approval duration: 6 months

C. Rheumatoid Arthritis (must meet all):

1. Diagnosis of RA;
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, unless contraindicated or clinically significant adverse effect are experienced;
   b. If intolerance or contraindication to MTX (*see Appendix C*), 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 contraindicated or clinically significant adverse effect are experienced;
5. Failure of etanercept *(Enbrel® is preferred)* and adalimumab *(Humira is preferred)*, each used for ≥ 3 consecutive months, unless contraindicated or clinically significant adverse effects are experienced;
   **Prior authorization is required for etanercept and adalimumab*
6. Prescribed concomitantly with MTX, or another DMARD if intolerance or contraindication to MTX;
7. If request is for Remicade, member has experienced clinically significant adverse effects or has a contraindication to excipients from Inflectra and Renflexis;
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.

Approval duration: 6 months

D. 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. Failure of etanercept *(Enbrel is preferred)* and adalimumab *(Humira is preferred)*, each used for ≥ 3 consecutive months, unless contraindicated or clinically significant adverse effects are experienced;
   **Prior authorization is required for etanercept and adalimumab*
6. If request is for Remicade, member has experienced clinically significant adverse effects or has a contraindication to excipients from Inflectra and Renflexis;
7. Dose does not exceed 5 mg/kg at weeks 0, 2, and 6, followed by maintenance dose of 5 mg/kg every 6 weeks.

Approval duration: 6 months

E. 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. Member meets one of the following (a or b):
   a. Failure of ≥ 3 consecutive month trial of MTX at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
   b. If intolerance or contraindication to MTX (*see Appendix C*), failure of a ≥ 3 consecutive month trial of cyclosporine, sulfasalazine, or leflunomide at up to maximally indicated doses, unless contraindicated or clinically significant adverse effect are experienced;
5. Failure of etanercept *(Enbrel is preferred)* and adalimumab *(Humira is preferred),* each used for ≥ 3 consecutive months, unless contraindicated or clinically significant adverse effects are experienced;
   **Prior authorization is required for etanercept and adalimumab*
6. If request is for Remicade, member has experienced clinically significant adverse effects or has a contraindication to excipients from Inflectra and Renflexis;
7. Dose does not exceed 5 mg/kg at weeks 0, 2, and 6, followed by maintenance dose of 5 mg/kg every 8 weeks.

Approval duration: 6 months

F. Plaque Psoriasis (must meet all):

1. Diagnosis of PsO;
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, unless contraindicated or clinically significant adverse effects are experienced;
   b. If intolerance or contraindication to MTX (*see Appendix C*), failure of a ≥ 3 consecutive month trial of cyclosporine or acitretin at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
5. Failure of a ≥ 3 consecutive month trial of adalimumab (*Humira is preferred*), unless contraindicated or clinically significant adverse effects are experienced;
   **Prior authorization is required for adalimumab*
6. If request is for Remicade, member has experienced clinically significant adverse effects or has a contraindication to excipients from Inflectra and Renflexis;
7. Dose does not exceed 5 mg/kg at weeks 0, 2, and 6, followed by maintenance dose of 5 mg/kg every 8 weeks.

Approval duration: 6 months

B. Other diagnoses/indications

1. Refer to HIM.PHAR.21 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 Centene benefit or member has previously met all initial approval criteria;
2. Member is responding positively to therapy;
3. If request is for a dose increase, new regimen does not exceed one of the following (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/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/Inflectra/Renflexis;
            2) Current dosing frequency is < every 8 weeks: member has received at least 2 doses of Remicade/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. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to HIM.PHAR.21 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 – HIM.PHAR.21 or evidence of coverage documents.

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
MTX: methotrexate
NSAID: non-steroidal anti-inflammatory drug
PsA: psoriatic arthritis
PsO: psoriasis
RA: rheumatoid arthritis
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*, UC*** 1.5 – 2 mg/kg/day PO	2.5 mg/kg/day
corticosteroids	**CD*** 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	Various
Cuprimine® (d-penicillamine)	**RA*** <u>Initial dose:</u> 125 or 250 mg PO QD <u>Maintenance dose:</u> 500 – 750 mg/day PO QD	1,500 mg/day
cyclosporine (Sandimmune®, Neoral®)	**PsO** 2.5 mg/kg/day PO divided BID **PsA*** 2.5 – 3 mg/kg/day PO QD **RA** 2.5 – 4 mg/kg/day PO divided BID	PsO, RA: 4 mg/kg/day PsA: 3 mg/kg/day
hydroxychloroquine (Plaquenil®)	**RA*** <u>Initial dose:</u> 400 – 600 mg/day PO QD <u>Maintenance dose:</u> 200 – 400 mg/day PO QD	600 mg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
leflunomide (Arava®)	**PsA*** 100 mg/day PO loading dose for 3 days followed by 20 mg/day PO QD **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 PO
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 **PsA*** 7.5 – 15 mg/week PO **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 PO
Ridaura® (auranofin)	**RA** 6 mg PO QD or 3 mg PO BID	9 mg/day (3 mg TID)
sulfasalazine (Azulfidine®)	**PsA*** 2 g/day PO QD **RA** 2 g/day PO in divided doses **UC** <u>Initial dose:</u> *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	PsA: 5 g/day RA: 3 g/day UC: 4 g/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	Maintenance 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
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, PsA** 40 mg SC every other week **CD, 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 **PsO** Initial dose: 80 mg SC Maintenance dose: 40 mg SC every other week starting one week after initial dose **RA** 40 mg SC every other week (may increase to once weekly)	AS, PsA, UC: 40 mg every other week RA: 40 mg/week

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: General Information

- Contraindications:
  - Remicade doses > 5 m/kg should not be administered to patients with moderate to severe heart failure. Remicade doses of 10 mg/kg were shown to be associated with an increased incidence of death and hospitalization due to worsening heart failure in clinical trials.
- Ankylosing Spondylitis:
  - Several AS treatment guidelines call for a trial of 2 or 3 NSAIDs prior to use of an anti-TNF agent. A two year trial showed that continuous NSAID use reduced radiographic progression of AS versus on demand use of NSAID.
- 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

V. References

1. Remicade Prescribing Information. Horsham, PA: Janssen Biotech, Inc.; October 2017. Available at http://www.remicade.com/shared/product/remicade/prescribing-information.pdf. Accessed February 27, 2018.
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6. Smolen JS, Landewé R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis. 2014; 73: 492-509.

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8. Sandborn WJ. Crohn's Disease Evaluation and Treatment: Clinical Decision Tool. Gastroenterology 2014; 147: 702-705.
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11. Menter A, Korman NJ, Elmets CA, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 6: Guidelines of care for the treatment of psoriasis and psoriatic arthritis: case-based presentations and evidence-based conclusions. J Am Acad Dermatol. 2011;65(1):137-174.
12. Menter A, Gottlieb A, Feldman SR, et al. Guidelines for the management of psoriasis and psoriatic arthritis. Section 1: Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. J Am Acad Dermatol. 2008;58(5):826-850.
13. Bernell O, Lapidus A, Hellers G. Risk Factors for Surgery and Postoperative Recurrence in Crohn's Disease. Annals of Surgery. 2000; 231(1): 38-45.

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
Q5102	Injection, infliximab, biosimilar, 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
Policy created.	02.27.18	05.18
No significant changes: Inflectra and Renflexis added to policy. Preferencing for Inflectra and Renflexis added.	07.11.18	

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.

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