Clinical Policy: Infliximab (Remicade, Inflectra, Renflexis)

Reference Number: CP.PHAR.254
Effective Date: 07/16
Last Review Date: 07/17

Coding Implications
Revision Log

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

Description

Infliximab (Remicade®), infliximab-dyyb (Inflectra®) and infliximab-abda (Renflexis™) are chimeric monoclonal antibodies that binds to human tumor necrosis factor alpha (TNFα), thereby interfering with endogenous TNFα activity. Elevated TNFα levels have been found in involved tissues/fluids of patients with rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), plaque psoriasis (PsO), Crohn's disease (CD) and ulcerative colitis (UC).

FDA approved indication

Remicade, Inflectra* and Renflexis* are indicated for the treatment of:

- Crohn's Disease: 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. Remicade is indicated for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing CD.
- Pediatric Crohn's Disease: 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: 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 Ulcerative Colitis (Remicade only): 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 in combination with methotrexate: Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active RA.
- Ankylosing Spondylitis: Reducing signs and symptoms in patients with active AS.
- Psoriatic Arthritis: Reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in patients with PsA.
- Plaque Psoriasis: 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.

**Inflectra and Renflexis are FDA approved for all indications above except pediatric UC.*

Policy/Criteria

Provider must submit documentation (which may include office chart notes and lab results) 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 and (a or b):
   a. Member is identified as moderate/high risk based on one of the following:
      i. Age at initial diagnosis < 30 years;
      ii. Extensive anatomic involvement (e.g., ileocecal disease, continuous ileocolonic disease, small bowel disease);
      iii. Perianal and/or severe rectal disease;
      iv. Deep ulcers;
      v. Prior surgical resection;
      vi. Stricturing and/or penetrating disease;
   b. Member has failed both of the following, unless contraindicated or clinically significant adverse effects are experienced (i and ii):
      i. An immunomodulator (e.g., azathioprine, mercaptopurine (6MP), methotrexate (MTX)) used for ≥ 3 months;
      ii. Adalimumab *(Humira is preferred)* used for ≥ 3 consecutive months;
      **Prior authorization is required for adalimumab*
2. Prescribed by or in consultation with a gastroenterologist;
3. Age ≥ 6 years;
4. If request is for Remicade or Renflexis, member has failed or experienced clinically significant adverse effects from Inflectra;
5. Tuberculosis (TB) test within the past 12 months is negative, or if positive, active TB has been ruled out and the member has received treatment for latent TB infection;
6. Dose does not exceed the following:
   a. Initial: 5 mg/kg at weeks 0, 2, and 6;
   b. Maintenance: adults - 10 mg/kg every 8 weeks; children and adolescents – 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 gastroenterologist;
3. Age ≥ 6 years;
4. Failure of a thiopurine (e.g., azathioprine, 6MP), used for ≥ 3 months, unless contraindicated or clinically significant adverse effects are experienced;
5. If age is ≥ 18 years, member has failed or experienced clinically significant adverse effects to Inflectra;
6. TB test within the past 12 months is negative, or if positive, active TB has been ruled out and the member has received treatment for latent TB infection;
7. Dose does not exceed the following:
   a. Initial: 5 mg/kg at weeks 0, 2, and 6;
   b. Maintenance: 5 mg/kg every 8 weeks.

Approval duration: 6 months

C. Rheumatoid Arthritis (must meet all):
1. Diagnosis of RA per American College of Rheumatology (ACR) criteria (refer to *Appendix B*);
2. Prescribed by or in consultation with a rheumatologist;
3. Age ≥ 18 years;
4. If request is for Remicade or Renflexis, member has failed or experienced clinically significant adverse effects to Inflectra;
5. Member meets one of the following (a or b):
   a. Failure of MTX for ≥ 3 consecutive months unless contraindicated or clinically significant adverse effect are experienced;
   b. If intolerance or contraindication to MTX, failure of sulfasalazine, leflunomide, or hydroxychloroquine for ≥ 3 consecutive months unless contraindicated or clinically significant adverse effect are experienced;
6. 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*
7. TB test within the past 12 months is negative, or if positive, active TB has been ruled out and the patient has received treatment for latent TB infection;
8. Dose does not exceed the following:
   a. Initial: 3 mg/kg at weeks 0, 2, and 6;
   b. Maintenance: 10 mg/kg every 4 weeks.

Approval duration: 6 months

D. Ankylosing Spondylitis (must meet all):
1. Diagnosis of active AS;
2. Prescribed by or in consultation with a rheumatologist;
3. Age ≥ 18 years;
4. If request is for Remicade or Renflexis, member has failed or experienced clinically significant adverse effects to Inflectra;
5. Failure of at least TWO non-steroidal anti-inflammatory drugs (NSAIDs) each trialed for ≥ 4 weeks unless contraindicated or clinically significant adverse effect are experienced;
6. 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*
7. TB test within the past 12 months is negative, or if positive, active TB has been ruled out and the member has received treatment for latent TB infection;
8. Dose does not exceed the following:
   a. Initial: 5 mg/kg at weeks 0, 2, and 6;
   b. Maintenance: 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. If request is for Remicade or Renflexis, member has failed or experienced clinically significant adverse effects to Inflectra;
5. Member meets one of the following (a or b):
   a. Failure of MTX for ≥ 3 consecutive months unless contraindicated or clinically significant adverse effect are experienced;
   b. If intolerance or contraindication to MTX, sulfasalazine, leflunomide, or cyclosporine for ≥ 3 consecutive months unless contraindicated or clinically significant adverse effect are experienced;
6. 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*
7. TB test within the past 12 months is negative, or if positive, active TB has been ruled out and the member has received treatment for latent TB infection;
8. Dose does not exceed the following:
   a. Initial: 5 mg/kg at weeks 0, 2, and 6;
   b. Maintenance: 5 mg/kg every 8 weeks.

Approval duration: 6 months

F. Plaque Psoriasis (must meet all):

1. Diagnosis of chronic severe (i.e., extensive and/or disabling) PsO and one or more of the following (a or b):
   a. Greater than 5% of body surface area is affected;
   b. Involvement of palms, soles, face/neck, body folds, or genitalia;
2. Prescribed by or in consultation with a dermatologist or rheumatologist;
3. Age ≥ 18 years;
4. If request is for Remicade or Renflexis, member has failed or experienced clinically significant adverse effects to Inflectra;
5. Failure of phototherapy and a topical therapy (e.g., calcipotriene, coal tar preparations, medium-to-high potency corticosteroids, anthralin, tazarotene), unless contraindicated or clinically significant adverser effects are experienced;
6. Failure of at least one systemic therapy (e.g., MTX, cyclosporine, acitretin, thioguanine) for ≥ 3 consecutive months unless contraindicated or clinically significant adverse effect are experienced;
7. TB test within the past 12 months is negative, or if positive, active TB has been ruled out and the member has received treatment for latent TB infection;
8. Dose does not exceed the following:
   a. Initial: 5 mg/kg at weeks 0, 2, and 6;
   b. Maintenance: 5 mg/kg every 8 weeks.

Approval duration: 6 months

G. Other diagnoses/indications: Refer to CP.PHAR.57 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Approval

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, member has not responded adequately to current dose and requested dose does not exceed the following
    a. RA and CD: 10mg/kg/dose;
    b. All other indications: 5mg/kg/dose;
4. Prescribed regimen for Remicade/Inflectra does not exceed the following (a, b or c):
    a. AS: dosing frequency of every 6 weeks;
    b. RA: dosing frequency of every 4 weeks; if the request represents an increase in dosing frequency from the current regimen, documentation supports both of the following (i and ii):
        i. Member has had an inadequate response to adherent use of Remicade/Inflectra concurrently with MTX or another disease-modifying antirheumatic drug (DMARD);
        ii. 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 Remicade/Inflectra;
            b) Current dosing frequency is < every 8 weeks: member has received at least 2 doses of Remicade/Inflectra at the current dosing frequency;
    c. All other indications: dosing frequency of every 8 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 health plan benefit and documentation supports positive response to therapy.

Approval duration: Duration of request or 6 months (whichever is less); or

2. Refer to CP.PHAR.57 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

6MP: mercaptopurine
AS: ankylosing spondylitis
CCP: citrullinated peptide
CD: Crohn's disease
CRP: C-reactive protein
DMARD: disease modifying antirheumatic drug
ESR: erythrocyte sedimentation rate
MTX: methotrexate
PsA: psoriatic arthritis
PsO: psoriasis
RA: rheumatoid arthritis
SC: subcutaneous
TB: tuberculosis
TNF: tumor necrosis factor
UC: ulcerative colitis

Appendix B: 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 normal ESR	1
D	**Duration of symptoms**	
	< 6 weeks	0
	≥ 6 weeks	1

Appendix C: Definition of MTX or disease-modifying antirheumatic drug (DMARD) failure
In RA, failure of MTX or DMARD is defined as ≤ 50% decrease in swollen joint count, ≤ 50% decrease in tender joint count, and ≤ 50% decrease in ESR, or ≤ 50% decrease in CRP.

IV. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
RA	3 mg/kg IV initially and at weeks 2 and 6, then every 8 weeks	10 mg/kg every 4 weeks
AS	5 mg/kg IV initially and at weeks 2 and 6, then every 6 weeks	5 mg/kg every 6 weeks
CD, UC, PsO, PsA	5 mg/kg IV initially and at weeks 2 and 6, then every 8 weeks	CD (adults): 10 mg/kg every 8 weeks PsO, PsA, UC, CD (children and adolescents): 5 mg/kg every 8 weeks

V. Product Availability

Drug	Availability
infliximab (Remicade), infliximab-dyyb (Inflectra) infliximab-abda (Renflexis)	Single-use vial: 100 mg

VI. References

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15. Gladman DD, Ritchlin C. Treatment of psoriatic arthritis. In: UpToDate, Waltham, MA: Walters Kluwer Health; 2016. Available at www.UpToDate.com. Accessed June 16, 2016.

16. Feldman SR. Treatment of psoriasis. In: UpToDate, Waltham, MA: Walters Kluwer Health; 2016. Available at www.UpToDate.com. Accessed June 15, 2016.
17. Infliximab Drug Monograph. Clinical Pharmacology. Accessed June 2017. http://www.clinicalpharmacology-ip.com.
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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
Q5102	Injection, infliximab, biosimilar, 10 mg

Reviews, Revisions, and Approvals	Date	Approval Date
Policy split from CP.PHAR.86.ArthritisTreatments, CP.PHAR.85.Psoriasis Treatments, CP.PHAR.87.IBD Treatment_4_ Added the biosimilar Inflectra (approved for all Remicade indications with the exception of pediatric UC). CD, UC, RA, PsA, AS, PsO: Removed criteria related to HBV, malignant disease, concomitant use with other biologics, and concurrent administration of live vaccines; added dosing. CD: modified criteria requiring failure of immunomodulator, corticosteroids or aminosalicylate to failure of "corticosteroid, with or without immunomodulator" per 2014 AGA Clinical decision tool. RA: changed age requirement to 18; modified criteria to require trial of MTX, unless contraindicated; added sulfasalazine and hydroxychloroquine as an alternative to MTX if contraindicated; Required trial of Humira AND Enbrel instead of one or the other. Added option for other DMARD if concomitant admin of MTX contraindicated. AS: added option of trial of a different biologic in addition to NSAIDs. Required trial of Humira AND Enbrel instead of one or the other. PsA: Added requirements for failure of a different biologic or 2 or more DMARDs, not including Otezla. PsO: removed duration of trial for topical and phototherapy; Added option for trial of a different biologic. Required trial of Humira and Enbrel, instead of previous requirement of Humira or Enbrel. Re-auth: combined into All Indications; added criteria for dosing and reasons to discontinue; for PsO changed efficacy criteria related to Psoriasis Area and Severity Index (PASI)-75 to general efficacy statement.	07/16	07/16

Reviews, Revisions, and Approvals	Date	Approval Date
Modified approval duration to 6 months for initial and 12 months for renewal.		
Added preferencing for Inflectra prior to allowing Remicade, except for UC patients aged 6-18. CD: Removed corticosteroid as an option for trial/failure. UC: removed aminosalicylates and corticosteroids as potential acceptable first-line therapies. PsA: Preferenced trial of MTX above other DMARDs. Specialist review by dermatologist, rheumatologist, and gastroenterologist.	11/16	12/16
Humira preferencing in pediatric Crohn's is removed.	03/17	
Converted to new template. Removed limitations based on labeled warnings and precautions. RA: modified the RA diagnostic criteria from requiring one or more of the following: ≥ 5 inflamed joints, elevated ESR and/or CRP; positive rheumatoid factor and/or anticyclic citrullinated peptide (CCP) antibodies; evidence of inflammation on plain radiography of the hands, wrists, or feet, such as osteopenia and/or periarticular swelling, to the ACR diagnostic criteria. PsA: changed option of contraindication to hydroxychloroquine to cyclosporine. PsO: removed redirection to Enbrel and Humira. AS: added prescriber restriction. CD: updated list of poor prognostic indicators. UC: change required trials form immunomodulator to specifically thiopurines and removed MTX as example of acceptable trial; removed redirection to Humira. Added Renflexis.	07/17	07/17

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.

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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.