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

Reference Number: ERX.SPA.160
Effective Date: 10.01.16
Last Review Date: 11.17 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®)], is a chimeric IgG1k monoclonal antibody targeted against tumor necrosis factor-alpha (TNF-alpha).

FDA Approved Indication(s)
Remicade, 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 disease 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 with moderately to severely active disease 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 disease 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 disease who have had an inadequate response to conventional therapy
- Rheumatoid arthritis (RA) in combination with methotrexate (MTX):
  - Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active disease
- Ankylosing spondylitis (AS):
  - Reducing signs and symptoms in patients with active disease
- Psoriatic arthritis (PsA):
  - Reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function
- Plaque psoriasis (PsO):
  - Treatment of adult patients with chronic severe (i.e., extensive and/or disabling) disease who are candidates for systemic therapy and when other systemic therapies are medically less appropriate

**Renflexis and Inflectra are approved for all of the above indications except for 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 Envolve Pharmacy Solutions™ 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 moderate-to-severe CD;
2. Prescribed by or in consultation with a gastroenterologist;
3. Age ≥ 6 years;
4. Failure of a trial of a thiopurine (6-mercaptopurine or azathiopurine) or MTX for ≥ 3 consecutive months, unless contraindicated or clinically significant adverse effects are experienced;
5. Failure of a trial of adalimumab (*Humira is preferred*) for ≥ 3 consecutive months unless contraindicated or clinically significant adverse effects are experienced;
   **Prior authorization is required for adalimumab*
6. Dose does not exceed 5 mg/kg at Week 0, 2, and 6, then every 8 weeks.

Approval duration: 6 months

B. Ulcerative Colitis (must meet all)**:**
1. Diagnosis of moderate-to-severe UC;
2. Prescribed by or in consultation with a gastroenterologist;
3. Age ≥ 6 years;
4. Failure of a trial of a thiopurine (i.e., azathioprine, 6-mercaptopurine);
5. If age ≥ 18 years, failure of a trial of adalimumab (*Humira is preferred*) for ≥ 3 consecutive months unless contraindicated or clinically significant adverse effects are experienced;
   **Prior authorization is required for adalimumab*
6. Dose does not exceed 5 mg/kg at Week 0, 2, and 6, then 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 trial of MTX (at up to maximally indicated doses) used for ≥ 3 consecutive months, unless contraindicated or clinically significant adverse effects are experienced;
   b. If intolerance or contraindication to MTX, failure of a trial of sulfasalazine or 1 other conventional DMARD (at up to maximally indicated doses) used for ≥ 3 consecutive months, unless contraindicated or clinically significant adverse effects are experienced (*see Appendix C*);
5. Failure of etanercept (*Enbrel is preferred*) AND adalimumab (*Humira is preferred*), each trialed 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. Dose does not exceed 3 mg/kg at Week 0, 2, and 6, then every 8 weeks.

Approval duration: 6 months

D. Ankylosing Spondylitis (must meet all)**:**
1. Diagnosis of active AS;
2. Age ≥ 18 years;
3. Prescribed by or in consultation with a rheumatologist;
4. Failure of at least two non-steroidal anti-inflammatory drugs (NSAIDs), each tried for at least 1 month at maximal recommended or tolerated anti-inflammatory doses, unless contraindicated or clinically significant adverse effects are experienced;
5. Failure of etanercept (*Enbrel is preferred*) AND adalimumab (*Humira is preferred*), each trialed for ≥ 3 consecutive months, unless contraindicated or clinically significant adverse effects are experienced;
   **Prior authorization is required for etanercept and adalimumab*
6. Dose does not exceed 5 mg/kg at Week 0, 2, and 6, then every 6 weeks.

Approval duration: 6 months

E. Psoriatic Arthritis (must meet all)**:**
1. Diagnosis of active 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 a trial of MTX used for ≥ 3 consecutive months, unless contraindicated or clinically significant adverse effects are experienced;
   b. If MTX is contraindicated, failure of a trial of leflunomide, sulfasalazine, or cyclosporine used for ≥ 3 consecutive months, unless contraindicated or clinically significant adverse effects are experienced;
5. Failure of etanercept (*Enbrel is preferred*) AND adalimumab (*Humira is preferred*), each trialed for ≥ 3 consecutive months, unless contraindicated or clinically significant adverse effects are experienced;
   **Prior authorization is required for etanercept and adalimumab*
6. Dose does not exceed 5 mg/kg at Week 0, 2, and 6, then every 8 weeks.

Approval duration: 6 months

F. Plaque Psoriasis (must meet all)**:**
1. Diagnosis of moderate-to-severe 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 trial of MTX at up to a dose of 15-20 mg/week used for ≥ 3 consecutive months, unless contraindicated or clinically significant adverse effects are experienced;
   b. If intolerance or contraindication to MTX, failure of a trial of cyclosporine or acitretin unless contraindicated or clinically significant adverse effects are experienced;
5. Failure of etanercept (*Enbrel is preferred*) AND adalimumab (*Humira is preferred*), each trialed for ≥ 3 consecutive months, unless contraindicated or clinically significant adverse effects are experienced;
   **Prior authorization is required for etanercept and adalimumab*
7. Dose does not exceed 5 mg/kg at Week 0, 2, and 6, then every 8 weeks.

Approval duration: 6 months

G. Other diagnoses/indications
1. 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 is responding positively to therapy (e.g., labs, sign/symptom reduction, no disease progression, no significant toxicity);
3. If request is for a dose increase, new regimen does not exceed the following:
   a. AS: 5 mg/kg every 6 weeks;
   b. CD: 5 mg/kg (10 mg/kg if age ≥ 18 years and inadequate response to current dose) every 8 weeks;
   c. RA: meets one of the following (i or ii):
      i. 3 mg/kg every 8 weeks;
      ii. If the request represents an increase in dose or dosing frequency (*only 1 may be increased at a time*) from the current regimen, does not exceed 10 mg/kg and/or every 4 weeks, and documentation supports both of the following (i and ii):
         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. PsA, PsO, UC: 5 mg/kg every 8 weeks.

Approval duration: 12 months

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

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

AS: ankylosing spondylitis
CD: Crohn's disease
DMARD: disease modifying anti-rheumatic drug
MTX: methotrexate
PsA: psoriatic arthritis
PsO: psoriasis
RA: rheumatoid arthritis
UC: ulcerative colitis

Appendix B: General Information

- 2010 ACR classification criteria for RA:

Classification criteria for RA (score-based algorithm: 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)		
		Score
A	**Joint involvement**	
	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	2
	High positive RF *or* high positive ACPA	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

- 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.
- 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 NSAID use.

- HS is sometimes referred to as: "acne inversa, acne conglobata, apocrine acne, apocrinitis, Fox-den disease, hidradenitis axillaris, HS, pyodermia sinifica fistulans, Velpeau's disease, and Verneuil's disease."
- In HS, Hurley stages are used to determine severity of disease. Hurley stage II indicates moderate disease, and is characterized by recurrent abscesses, with sinus tracts and scarring, presenting as single or multiple widely separated lesions. Hurley stage III indicates severe disease, and is characterized by diffuse or near-diffuse involvement presenting as multiple interconnected tracts and abscesses across an entire area.

Appendix C: Therapeutic Alternatives

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Ridaura® (auranofin)	Rheumatoid Arthritis 6 mg PO QD or 3 mg PO BID	9 mg/day (3 mg TID)
azathioprine (Imuran®)	Rheumatoid Arthritis 1 mg/kg PO given as a single dose or twice daily	2.5 mg/kg/day
Cuprimine® (d-penicillamine)	Rheumatoid Arthritis Initial dose: 125 or 250 mg PO Maintenance dose: 500-750 mg/day PO	1000 mg to 1500 mg QD
hydroxychloroquine (Plaquenil®)	Rheumatoid Arthritis Initial dose: 400-600 mg PO QD Maintenance dose: 200-400 mg PO QD	600 mg/day
methotrexate (Rheumatrex®)	Rheumatoid Arthritis 7.5 mg/week PO or 2.5 mg PO Q12hr for 3 doses/week Plaque Psoriasis 10 to 25 mg/week IM, IV or PO	30 mg/week
sulfasalazine (Azulfidine®)	Rheumatoid Arthritis 2 g/day PO in divided doses	3 g/day
Soriatane® (acitretin)	Plaque Psoriasis 25 or 50 mg PO daily	50 mg/day
cyclosporine	Plaque Psoriasis 2.5 - 4 mg/kg/day PO divided BID	4 mg/kg/day

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
CD	5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. Some adult patients who initially respond to treatment may benefit from increasing the dose to 10 mg/kg if they later lose their response	10 mg/kg/dose IV
Pediatric CD	5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks	≥ 6 years old: 5 mg/kg/dose
UC	5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks	5 mg/kg/dose IV
RA	In conjunction with MTX: 3 mg/kg at 0, 2 and 6 weeks, then 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/dose IV
AS	5 mg/kg at 0, 2 and 6 weeks, then every 6 weeks	5 mg/kg/dose IV
PsA	5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks	5 mg/kg/dose IV

Indication	Dosing Regimen	Maximum Dose
PsO	5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks	5 mg/kg/dose IV

VI. Product Availability

Drug Name	Availability
Infliximab (Remicade)	Vial: 100 mg lyophilized infliximab in a 20 mL vial for IV infusion
Infliximab-dyyb (Inflectra)	Vial: 100 mg of lyophilized infliximab-dyyb in a 20 mL vial for IV infusion
Infliximab-abda (Renflexis)	Vial: 100 mg of lyophilized infliximab-abda in a 20 mL vial for IV infusion

VII. References

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12. Renflexis Prescribing Information. Kenilworth, NJ: Merck & Co; April 2017. Available at: https://www.merck.com/product/usa/pi_circulars/r/renflexis/renflexis_pi.pdf. Accessed October 2, 2017.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy split from USS.SPMN.24 Irritable Bowel Disease (IBD) Treatments, USS.SPMN.41 Psoriasis Treatments, and USS.SPMN.44 Rheumatoid Arthritis and Ankylosing Spondylitis Treatments. Converted to new template. Added the biosimilar Inflectra (approved for all Remicade indications with the	08.16	09.16

Reviews, Revisions, and Approvals	Date	P&T Approval Date
exception of pediatric UC). Removed all safety criteria. Added dosing per PI. Modified approval duration to 6 months for initial and 12 months for renewal with the exception of UC which is 2 months (time to clinical remission per PI) and 12 months. Shortened background section. 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. For PsO, changed efficacy criteria related to Psoriasis Area and Severity Index (PASI)-75 to general efficacy statement.		
For all trial/failure requirements, indicated that member can also meet criteria if intolerant (as opposed to just contraindicated) to therapy in question. Modified the following initial criteria sets: -All indications: removed requirement of additional biologic; -CD: modified trial/failure requirement to indicate an immunomodulator (as opposed to a corticosteroid with or without an immunomodulator) must be trialed. -UC: indicated that disease must be moderately to severely active. Removed option for trial/failure of corticosteroid and aminosalicylate. -RA: indicated that disease must be moderately to severely active. -PsA: modified trial/failure requirement- instead of requiring 2 or more nonbiologic DMARDs (such as cyclosporine, sulfasalazine, azathioprine, hydoxychloroquine), criteria now requires MTX; if MTX is contraindicated, then cyclosporine, sulfasalazine, leflunomide, cyclosporine, or azathioprine may be trialed. -PsO: indicated that disease must be chronic and severe.	11.16	12.16
For RA, modified re-auth approval duration to allow dosing frequency up to every 4 weeks for those with inadequate response to every 8 week dosing per PI.	05.17	
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	10.02.17	11.17

Reviews, Revisions, and Approvals	Date	P&T Approval Date
-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; -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.		

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.