BlueCross BlueShield of Arizona
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MEDICAL COVERAGE GUIDELINES
SECTION: DRUGS

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REMICADE® (infliximab)

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Medical Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Medical Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Medical Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

Description:

Remicade (infliximab) is a tumor-necrosis factor (TNF) inhibitor. TNF inhibitors are naturally occurring proteins involved in the body's normal immune responses. Overproduction of TNF can cause inflammation and tissue damage. TNF inhibition may ease certain inflammatory disease symptoms and prevent disease progression.

REMICADE (infliximab)

Description: (cont.)

Remicade (infliximab) is generally given to individuals who fail or have had an inadequate response to conventional therapy. However, not all individuals respond to infliximab and some individuals lose response over time. An estimated one-third of individuals do not respond to induction therapy (primary nonresponse), and among initial responders, response wanes over time in approximately 20% to 60% of individuals (secondary nonresponse). The reason for therapeutic failures remains a matter of debate. One proposed factor associated with loss of response is the production of antidrug antibodies, which accelerate clearance of the drug. The measurement of serum concentrations of infliximab and antibodies to infliximab have been investigated as a method to determine if an individual has developed antibodies to infliximab. Prometheus® Laboratories Inc. Anser™ IFX test is one test that measures serum concentrations of infliximab and antibodies to infliximab.

Definitions:

Adult: Age 18 years and older

REMICADE (infliximab) (cont.)

Criteria:

See Resources section for FDA-approved dosage.

- FDA-approved dosage of Remicade is considered ***medically necessary*** with documentation of **ALL** of the following:

1. **ONE** of the following:
   - Reducing signs and symptoms and inducing and maintaining clinical remission in moderately to severely active Crohn's disease in adults who have had an inadequate response to conventional therapy
   - Reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in fistulizing Crohn's disease in adults
   - Reducing signs and symptoms and inducing and maintaining clinical remission in individuals 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy
   - Reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing and eliminating corticosteroid use in adults with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy
   - Reducing signs and symptoms and inducing and maintaining clinical remission in individuals 6 years of age and older with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy
   - Active ankylosing spondylitis, psoriatic arthritis or moderately to severely active rheumatoid arthritis in combination with methotrexate, who failed response to conventional therapy (unless otherwise contraindicated) or an inadequate response (as defined by prescribing provider)
   - Chronic severe (i.e., extensive and/or disabling) plaque psoriasis in adults who are candidates for systemic therapy and when other systemic therapies are medically less appropriate

2. No evidence of active serious infections including clinically important localized infections or sepsis when initiating or continuing therapy
3. Evidence of testing for latent tuberculosis before Remicade use and during therapy and any treatment for latent infection has been initiated prior to Remicade therapy
4. Evidence of ongoing monitoring in individuals who are known hepatitis B carriers for reactivation of this viral infection during Remicade therapy
5. No evidence of jaundice or marked liver enzyme elevations (e.g., $\geq$ 5 times the upper limit of normal)
6. No evidence of lupus-like syndrome or autoimmune hepatitis while on Remicade therapy
7. Evidence of close monitoring in individuals who have a history of or develop heart failure while on Remicade therapy
8. Remicade is not being used concurrently with anakinra (e.g., Kineret®), abatacept (e.g., Orencia®), toclizumab (e.g., Actemra®), other biological therapeutics, or live vaccines
9. Dosage is not greater than the FDA approved dosing for the labeled indication (refer to dosing table)

REMICADE (infliximab) (cont.)

Criteria: (cont.)

- The use of Remicade for the treatment of individuals 16 years of age or older with moderate to severe chronic pulmonary sarcoidosis is considered ***medically necessary*** with documentation of **ALL** the following:

    1. Failed response to treatment with at least two other regimens of conventional therapy of at least three months duration (unless otherwise contraindicated)
    2. Drug is being used to reduce signs and symptoms or to inhibit the progression of structural damage or to improve physical function
    3. No active or latent infection present (e.g., TB, cocci, hepatitis C) or presence of any type of wounds
    4. Not currently on immunomodulator therapy (e.g., Amevive®, Enbrel®, Humira®, Kineret or Orencia)
    5. No comorbidity of any demyelinating disease is present (e.g., multiple sclerosis, etc.)
    6. Dosage is not greater than initial dosing of 3 mg/kg administered intravenously at weeks 0, 2 and 6, followed by maintenance dosing of 3mg/kg administered intravenously every 6-8 weeks*.

- The use of Remicade is considered ***medically necessary*** for treatment of individuals 2 years of age and older with moderately to severely active polyarticular juvenile idiopathic arthritis with documentation of **ALL** of the following:

    1. Failed response to conventional therapy and to age-appropriate alternative TNF therapy (e.g., Enbrel, Humira, Orencia) (unless otherwise contraindicated)
    2. Drug is being used to reduce signs and symptoms of the disease
    3. No active or latent infection present (e.g., TB, cocci, hepatitis C), or presence of wounds of any type
    4. Not currently on immunomodulator therapy (e.g., Amevive, Enbrel, Humira, Kineret or Orencia)
    5. No comorbidity of any demyelinating disease is present (e.g., multiple sclerosis, etc.)
    6. Dosage is not greater than an initial dose of 3 mg/kg to 5 mg/kg intravenously followed in 2 weeks by another 3 mg/kg to 5 mg/kg intravenously then 3 mg/kg to 5 mg/kg intravenously every 4-8 weeks thereafter*

* Review by the clinical pharmacist, and/or medical director(s) and/or clinical advisor(s) is required if medication dosages differ from those listed above.

REMICADE (infliximab) (cont.)

Criteria: (cont.)

- The use of Remicade for the treatment of refractory uveitis is considered ***medically necessary*** with documentation of **ALL** of the following:

  1. Failed response to conventional therapy (unless otherwise contraindicated)
  2. No active or latent infection present (e.g., TB, cocci, hepatitis C), or presence of wounds of any type
  3. Not currently on immunomodulator therapy (e.g., Amevive, Enbrel, Humira, Kineret or Orencia)
  4. No comorbidity of any demyelinating disease is present (e.g., multiple sclerosis, etc.)

- Remicade for all other indications not previously listed or if above criteria not met is considered ***experimental or investigational*** based upon:

  1. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  2. Insufficient evidence to support improvement of the net health outcome, and
  3. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
  4. Insufficient evidence to support improvement outside the investigational setting.

Measurement of Antibodies to Infliximab:

- Measurement of antibodies to infliximab in an individual receiving treatment with infliximab, either alone or as a combination test which includes the measurement of serum infliximab levels, is considered ***experimental or investigational*** based upon:

  1. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  2. Insufficient evidence to support improvement of the net health outcome.

  Measurements include, *but are not limited to:*

  - Anser IFX test

REMICADE (infliximab) (cont.)

Resources:

1. 2.04.84 BCBS Association Medical Policy Reference Manual. Measurement of Serum Antibodies to Infliximab and Adalimumab. Re-issue date 09/12/2013, issue date 08/09/2012.

2. 5.01.15 BCBS Association Medical Policy Reference Manual. Infliximab. Re-issue date 10/10/2013, issue date 02/15/2002.

3. Biologics & Non-TNF Agents Potentially Winners in the New ACR Guidelines for Early & Experienced Rheumatoid Arthritis (RA) Patients *Specialty Pharma Journal.* Received 06/11/2012.

4. Remicade (infliximab) Treatment of Inflammatory Eye Disease. 04/17/2007 2007:1-11.

5. Remicade (infliximab) Treatment of Sarcoidosis. 07/06/2007 2007.

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8. Canadian Agency for Drugs and Technologies in Health. Technology Report Summary: Infliximab and Etanercept in Rheumatoid Arthritis: Timing, Dose Escalation, and Switching. *Technology Report Summaries.* Last Updated 04/18/2006, Accessed 06/05/2007 & 07/11/2007.

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REMICADE (infliximab) (cont.)

Resources (cont.)

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17. Genentech Barron H. Voluntary Market Withdrawal of Raptiva® (efalizumab) Patient Letter. 04/08/2009 2009.

18. Genentech Barron H. Voluntary Market Withdrawal of Raptiva® (efalizumab) Healthcare Professional Letter. 04/08/2009 2009.

19. Genentech Howell S. Voluntary Market Withdrawal of Raptiva® (efalizumab) Ancillary Provider Letter. 04/08/2009 2009.

20. Gerloni V, Pontikaki I, Gattinara M, Fantini F. Focus on adverse events of TNF{alpha} blockade in JIA in an open monocentric long-term prospective study of 163 patients. *Ann Rheum Dis.* 2007 Nov 2 2007.

21. Hale S, Lightman S. Anti-TNF therapies in the management of acute and chronic uveitis. *Cytokine.* 2006 Feb 21 2006;33(4):231-237.

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REMICADE (infliximab) (cont.)

Resources (cont.)

26. Norambuena RX, Mallol J, Rios MG, Quevedo RF, Quezada LA. Therapeutic effects of the anti-tumor necrosis factor monoclonal antibody, infliximab, in four children with refractory juvenile idiopathic arthritis. *Allergol Immunopathol (Madr).* 2007 Mar-Apr 2007;35(2):52-56.

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35. Wegscheider BJ, El-Shabrawi L, Weger M, et al. Adverse skin reactions to infliximab in the treatment of intraocular inflammation. *Eye.* 2007 Apr 2007;21(4):547-549.

REMICADE (infliximab) (cont.)

Resources (cont.)

Remicade Package Insert.

- FDA-approved indication and dosage:

Indication	Recommended Dose
Adults with: Crohn's disease Fistulizing Crohn's disease	5 mg/kg given as an IV induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg IV every 8 weeks thereafter. For adult patients who respond and then lose their response, consideration may be given to treatment with 10 mg/kg. Patients who do not respond by Week 14 are unlikely to respond with continued dosing and consideration should be given to discontinue REMICADE in these patients.
Pediatric Crohn's disease (age 6 years and older)	5 mg/kg IV induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg IV every 8 weeks thereafter.
Adult Ulcerative Colitis	5 mg/kg IV induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg IV every 8 weeks thereafter.
Pediatric Ulcerative Colitis (age 6 years and older)	5 mg/kg IV induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg IV every 8 weeks thereafter.
Rheumatoid Arthritis	3 mg/kg intravenous (IV) induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 3 mg/kg every 8 weeks thereafter. For patients who have an incomplete response, consideration may be given to adjusting the dose up to 10 mg/kg or treating as often as every 4 weeks bearing in mind that risk of serious infections is increased at higher doses. Remicade should be given in combination with methotrexate.
Ankylosing Spondylitis	5 mg/kg given as an IV induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg IV every 6 weeks thereafter.
Psoriatric Arthritis	5 mg/kg IV induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg IV every 8 weeks thereafter. Remicade can be used with or without methotrexate.
Adult Plaque Psoriasis	5 mg/kg given as an IV induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg IV every 8 weeks thereafter.

Adult: Age 18 years and older