

Corporate Medical Policy

Infliximab (Remicade)

File Name:	infliximab
Origination:	5/2002
Last CAP Review:	2/2011
Next CAP Review:	2/2012
Last Review:	6/2011

Description of Procedure or Service

Tumor necrosis factor (TNF) is a cytokine produced by macrophages and T cells. Its name is based on the original observations 25 years ago that TNF killed tumor cells in vitro. Further research has revealed that TNF has a broad spectrum of biologic activities; in particular, it is a key mediator of inflammation and is produced in response to infection and immunologic injury.

There are a number of TNF alpha blocking agents; etanercept (ENBREL®, Amgen); adalimumab (HUMIRA®, Abbott); certolizumab (CIMZIA®, UCB) administered via subcutaneous injection and infliximab (REMICADE® Centocor) administered via an intravenous (IV) infusion in the physician's office, outpatient setting, or infusion center. This policy focuses on infliximab that is administered in the physician's office and is thus typically adjudicated under the medical benefit.

The initial labeled indications for infliximab by the U.S. Food and Drug Administration (FDA) included treatment of rheumatoid arthritis, fistulizing Crohn's disease, and inducing remission in patients with moderately to severely active Crohn's disease that has had an inadequate response to conventional therapy. In 2002, the FDA approved an additional indication for maintaining clinical remission in Crohn's disease. Maintenance therapy is designed to prevent disease flares in patients with quiescent disease; the drugs most commonly used are azathioprine and 6-mercaptopurine. This new, labeled indication markedly broadens the clinical indications for patients with Crohn's disease. In December 2004, the FDA approved infliximab for the treatment of ankylosing spondylitis, and in early 2005, the FDA approved infliximab for the treatment of psoriatic arthritis. In September 2005, the FDA approved infliximab for the treatment of "reducing signs and symptoms, achieving clinical remission and mucosal healing, and eliminating corticosteroid use in patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy." In May 2006, the FDA approved infliximab for use in pediatric patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. In September 2006, FDA approved infliximab for patients with chronic severe (i.e., extensive and/or disabling) plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate. The need for close monitoring and regular follow-up visits with a physician is noted in the FDA approval.

On September 4, 2008, the FDA released an FDA Alert notifying healthcare professionals that histoplasmosis and other invasive fungal infections are not consistently recognized in patients taking tumor necrosis factor- α blockers (TNF blockers), Cimzia® (certolizumab pegol), Enbrel® (etanercept), Humira® (adalimumab), and Remicade® (infliximab). This situation has resulted in delays in appropriate treatment, sometimes resulting in death. The FDA will require the makers of the tumor necrosis factor- α blockers (TNF blockers) to further highlight the information about the risk of invasive fungal infections, such as histoplasmosis, in the Boxed Warning and Warnings sections of the drugs' prescribing information and the Medication Guide for patients. The FDA will also require that the makers of the TNF blockers educate prescribers about this risk.

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*****Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

Policy

BCBSNC will provide coverage for Remicade® (infliximab) when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

Infliximab may be subject to prior review requirements.

When Infliximab (Remicade) is covered

Remicade® (infliximab) may be medically necessary when both of the following criteria are met.

1. Remicade® (infliximab) is being used for one of the following indications:
 - a. to reduce the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing Crohn's disease; **or**
 - b. to reduce signs or symptoms or maintain clinical remission of moderately to severely active Crohn's disease in patients; **or**
 - c. when used alone or in combination with methotrexate to reduce the signs and symptoms of moderate to severe rheumatoid arthritis, rapidly advancing progressive rheumatoid arthritis, or psoriatic arthritis; **or**
 - d. ankylosing spondylitis refractory to conventional therapies (inadequate symptom relief from other treatments such as NSAIDs, COX-2 inhibitors, or methotrexate, unless unable to take these drugs); **or**
 - e. as treatment of severe plaque type psoriasis as evidenced by psoriatic plaques covering at least 10% of the body surface and have failed prior treatment with psoralen-UVA or other systemic therapies (refractory to conventional therapies); **or**
 - f. moderate to severe ulcerative colitis where the patient has inadequate response to conventional treatment such as aminosalicylates, corticosteroids, or immunosuppressants (unless unable to tolerate these drugs); **and**
2. The patient has no contraindications to the use of Remicade® (infliximab), including:
 - a. Class III or IV Congestive Heart Failure, **or**
 - b. Untreated active or latent tuberculosis.

When Infliximab (Remicade) is not covered

Other uses of infliximab are considered **investigational**, including, but not limited to:

1. Graft-versus-host disease (GVHD), juvenile rheumatoid arthritis (JRA), juvenile idiopathic arthritis-associated uveitis, polyarteritis nodosa, Bechet's syndrome, sarcoidosis, and systemic lupus erythematosus.
2. When used in combination with other biologics such as Enbrel® (etanercept), Kineret (anakinra),

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Orencia® (abatacept), Rituxan® (rituximab), or Humira® (adalimumab).

Policy Guidelines

Initial treatment is typically administered in a three-dose induction. Continued treatment may be considered when the member has shown biological response to treatment as evidenced by any of the disease assessment tools. Maintenance therapy is given typically every 6 - 8 weeks.

According to the Food and Drug Administration (FDA) approved labeling for Infliximab, doses should not exceed the following:

1. **Rheumatoid arthritis:** Max 10mg/kg every 4 weeks; allow 3-5 mg/kg at 0, 2, 6 weeks as part of initial therapy only.
2. **Crohn's disease:** Max 10 mg/kg every 8 weeks (or 5mg/kg every 4 weeks); allow 5mg/kg at 0, 2, 6 weeks as part of initial therapy only.
3. **Ulcerative colitis:** Max 5 mg/kg every 8 weeks; allow 5mg/kg at 0, 2, 6 weeks as part of initial therapy only.
4. **Ankylosing spondylitis:** Max 5mg/kg every 6 weeks; allow 5mg/kg at 0, 2, 6 weeks as part of initial therapy only.
5. **Psoriatic arthritis:** Max 5mg/kg every 8 weeks; allow 5mg/kg at 0, 2, 6 weeks as part of initial therapy only.
6. **Plaque psoriasis:** Max 5mg/kg every 8 weeks; allow 5mg/kg at 0, 2, 6 weeks as part of initial therapy only.

The approved labeling does not describe circumstances in which dosages above these maximum doses would be considered safe and effective.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: J1745

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

BCBSA Medical Policy Reference Manual, 2/15/2002; 5.01.15.

2002 USPDI - 22nd Edition, Volume 1; pps. 1698-1701.

BCBSA Medical Policy Reference Manual, 10/8/2002; 5.01.15

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2003 USPDI - 23rd Edition, Volume 1; pps. 1537-1540

Specialty Matched Consultant Advisory Panel - 3/2003

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.15, 11/9/04

Specialty Matched Consultant Advisory Panel, 2/2005

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.15, 9/27/05

Specialty Matched Consultant Advisory Panel, 1/2007

Centocor, Inc. Understanding Remicade, product information. Retrieved 3/14/08 from <http://www.remicade.com/remicade/global/understanding/understanding.html>

Senior Medical Director review, 3/20/2008

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.15, 6/14/07

Specialty Matched Consultant Advisory Panel, 1/2009

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.15, 1/8/2009

Specialty Matched Consultant Advisory Panel, 1/2010

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.15, 1/8/2009

Specialty Matched Consultant Advisory Panel Review 2/2011

<http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM193310.pdf>

Policy Implementation/Update Information

5/2002	Original policy issued.
8/2002	Revised sections under when it is covered and when it is not covered for clarity. Revised the policy guidelines for clarity. Format changes.
10/2002	Revised the Policy Guidelines section regarding USPDI and FDA indications. System coding changes.
01/2003	System coding changes.
3/2003	Specialty Matched Consultant Advisory Panel review 3/2003. Revised under "when it is covered" to include maintenance of clinical remission for specific indications. Statements revised under "policy guidelines" section.
4/04	Billing/Coding section updated for consistency.
3/17/05	Specialty Matched Consultant Advisory Panel meeting 2/24/2005. Added new indications in "When Covered" section; i.e. "as maintenance of remission in Crohn's disease". Changed language in i.d. to remove requirement of "inadequate response to Methotrexate or other first line disease-modifying agents (e.g., Imuran, Ridaura, Plaquenil, Cuprimine, Azulfidine, or Arava)". Added "i.e. Ankylosing spondylitis refractory to conventional therapies; or 1.f. Psoriatic arthritis refractory to conventional therapies". Under the "When Not Covered" section added "Other off-label uses are considered investigational,

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including but not limited to, treatment of ulcerative colitis, the dermatologic manifestations of, and polyarteritis nodosa." Added "Ankylosing Spondylitis, Psoriatic Arthritis, DRU4120" to Key Word section. References added.

- 12/15/05 Updated policy with new FDA-labeled indication of acute ulcerative colitis. Added Off-label use for with criteria to "When Covered" section. Added to "Policy Guidelines" section that "Infliximab is typically administered initially in a three-dose induction regimen every 3 weeks, followed by maintenance therapy every 8 weeks." References added.
- 9/18/06 Medical Policy changed to Evidence Based Guideline.
- 2/26/07 Specialty Matched Consultant Advisory Panel review 1/29/2007. Clarified #2 under the "When Not Recommended" section to read; "Other off-label uses not indicated as appropriate above, including but not limited to polyarteritis nodosa." References added.
- 4/1/08 Evidence Based Guideline converted to Medical Policy. Additional information provided in "Description" and "Policy Guideline" section. Additional indications added to "When Covered" section; "1.c. when used alone or in combination with Methotrexate to reduce the signs and symptoms of moderate to severe rheumatoid arthritis, rapidly advancing progressive rheumatoid arthritis, or psoriatic arthritis;" and "1.h. mild ulcerative colitis where the patient has inadequate response to conventional treatment such as aminosalicylates, corticosteroids, or immunosuppressants (unless unable to tolerate these drugs)". References added. Senior Medical Director review, 3/20/2008. Notification given April 1, 2008. Policy effective 7/1/2008.
- 11/3/08 Added "Class III or IV Congestive Heart Failure" to 2a. under the "When Covered" section. Revised "Policy Guidelines" section.
- 3/2/09 Specialty Matched Consultant Advisory Panel review 1/28/2009. No change in policy statement. Removed the word "mild" from 1.g. in the "When Covered" section. References added. (btw)
- 2/2/10 Specialty Matched Consultant Advisory Panel review 1/5/2010. Added information to the "When Covered" section; "1. a. to reduce the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing Crohn's disease". References added. (btw)
- 6/22/10 Policy Number(s) removed (amw)
- 3/15/11 Specialty Matched Consultant Advisory Panel review 2/2011. Removed medical term definitions. References added. (lpr)
- 7/1/11 Added quantity limitations to Policy Guidelines. Medical director review 6/2011. Changed dosage information in quantity limitations under Policy Guidelines for rheumatoid arthritis. New statement "Max 10mg/kg every 4 weeks instead of Max 10mg/kg every 8 weeks." Reviewed by Sr. Medical Director. Notification date 7/1/11 for effective date 10/1/2011. (lpr)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.
