

Corporate Medical Policy

Infliximab (Remicade[®]) and Infliximab Biosimilars

File Name:	infliximab
Origination:	5/2002
Last CAP Review:	2/2020
Next CAP Review:	2/2021
Last Review:	2/2020

Description of Procedure or Service

Infliximab (Remicade[®]) and infliximab biosimilars [infliximab-dyyb (Inflextra[™]), infliximab-abda (Renflexis[™]), infliximab-qbtx (Ixifi[™]), and infliximab-axxq (Avsola[™])] are tumor necrosis factor (TNF) alpha blocking agents approved by the U.S. Food and Drug Administration for the treatment of rheumatoid arthritis, Crohn's disease, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis and ulcerative colitis. Infliximab is administered via intravenous infusion.

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[®]), adalimumab (Humira[®]), certolizumab (Cimzia[®]) administered via subcutaneous injection, golimumab (Simponi[®]) administered subcutaneously or intravenously, and infliximab (Remicade[®]) administered via an intravenous (IV) infusion.

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. In 2011, the FDA approved infliximab for use in pediatric patients ages 6 years and older for the treatment of ulcerative colitis.

The FDA requires notification to prescribers of invasive fungal infections and monitoring for malignancies with use of TNA blockers. In addition, in March 2013, the FDA issued warnings and precautions against concurrent administration of infliximab with other biological agents.

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In March 2013, the FDA issued further warnings and precautions regarding malignancies and concurrent administration of infliximab with other biological agents. For concurrent administration with other biological therapeutics, current prescribing information states, “The concomitant use of Remicade with these biologics is not recommended because of the possibility of an increased risk of infection.”

In April 2016, Inflectra™ (infliximab-dyyb) was approved by the FDA through the biologics license application process as a biosimilar to Janssen Biotech’s Remicade®. Inflectra™ is approved for the same indications as Remicade®.

In April 2017, Renflexis™ (infliximab-abda) was approved by the FDA through the biologics license application process as a biosimilar to Janssen Biotech’s Remicade®. Renflexis™ is approved for the same indications as Remicade®.

In December 2017, Ixifi™ (infliximab-qbtx) was approved by the FDA through the biologics license application process as a biosimilar to Janssen Biotech’s Remicade®. Ixifi™ is approved for the same indications as Remicade® with the exception of pediatric ulcerative colitis.

In December 2019, Avsola™ (infliximab-axxq) was approved by the FDA through the biologics license application process as a biosimilar to Janssen Biotech’s Remicade®. Avsola™ is approved for the same indications as Remicade®.

Related Medical Policies:

Abatacept (Orencia)
Golimumab (Simponi Aria)
Rituximab for the Treatment of Rheumatoid Arthritis
Tocilizumab (Actemra)

Related Pharmacy Policies:

Humira®

******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 infliximab (Remicade®) and infliximab biosimilars (infliximab-dyyb, infliximab-abda, infliximab-qbtx, and infliximab-axxq) 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, infliximab-dyyb, infliximab-abda, infliximab-qbtx, and infliximab-axxq may be subject to prior review requirements.

When Infliximab (Remicade®) and Infliximab Biosimilars are covered

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

1. Remicade® (infliximab) is used for one of the following indications:

Crohn's Disease

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- To reduce the number of draining enterocutaneous and rectovaginal fistulas and maintain fistula closure in fistulizing Crohn's disease (adult patients); **OR**
- To reduce signs and symptoms and to induce and maintain clinical remission of moderately to severely active Crohn's disease (adult and pediatric patients); **OR**

Rheumatoid Arthritis

- When used in combination with methotrexate, or in combination with an alternative disease-modifying antirheumatic drug (e.g. leflunomide, sulfasalazine, hydroxychloroquine) if methotrexate is contraindicated or not tolerated, in patients with moderately to severely active rheumatoid arthritis to reduce signs and symptoms, inhibit progression of structural damage, and improve physical function; **OR**

Psoriatic Arthritis

- When used alone or in combination with methotrexate in patients with psoriatic arthritis to reduce signs and symptoms of active arthritis, inhibit progression of structural damage, and improve physical function; **OR**

Ankylosing Spondylitis

- To reduce signs and symptoms in patients with active 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**

Plaque Psoriasis

- To treat adult patients with chronic severe plaque psoriasis (as evidenced by psoriatic plaques covering at least 10% of the body surface) who have failed prior treatment with psoralen-UVA or UVB light therapy, or conventional systemic therapies (methotrexate, cyclosporine, Soriatane), or patient has a contraindication to these treatments; **OR**

Ulcerative Colitis

- To reduce signs and symptoms and to induce and maintain clinical remission in patients with moderately to severely active ulcerative colitis who have had inadequate response to conventional treatment such as aminosalicylates, corticosteroids, or immunosuppressants unless unable to tolerate these drugs (adult and pediatric patients); **OR**

Neurosarcoidosis; **OR**

Immune Checkpoint Inhibitor-Related Gastrointestinal Toxicity

- To treat moderate to severe diarrhea or colitis that develops during immune checkpoint inhibitor (PD-1, PD-L1) therapy, and
- Stool evaluation has ruled out an infectious etiology, and
- The gastrointestinal symptoms are steroid-refractory (see Policy Guidelines); **OR**

Hidradenitis Suppurativa

- To treat moderate to severe refractory hidradenitis suppurativa, and
- The patient has tried and failed, or is intolerant to, or has a clinical contraindication to adalimumab (Humira);

AND

2. The patient has no contraindications to the use of Remicade® (infliximab), including:

- Moderate to severe heart failure (New York Heart Association [NYHA] Functional Class III/IV), or

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- Previous severe hypersensitivity reaction to Remicade® or known hypersensitivity to any other component of the product or murine proteins.

Inflectra™ (infliximab-dyyb) may be medically necessary when the criteria listed above for Remicade® is met **and** the patient has tried and failed, or is intolerant to, or has a clinical contraindication to Remicade®.

Renflexis™ (infliximab-abda) may be medically necessary when the criteria listed above for Remicade® is met **and** the patient has tried and failed, or is intolerant to, or has a clinical contraindication to Remicade®.

Ixifi™ (infliximab-qbtx) may be medically necessary when the criteria listed above for Remicade® is met (with the exception of ulcerative colitis in pediatric patients) **and** the patient has tried and failed, or is intolerant to, or has a clinical contraindication to Remicade®.

Avsola™ (infliximab-axxq) may be medically necessary when the criteria listed above for Remicade® is met **and** the patient has tried and failed, or is intolerant to, or has a clinical contraindication to Remicade®.

When Infliximab (Remicade®) and Infliximab Biosimilars are not covered

Other uses of infliximab (Remicade®) and infliximab biosimilars (infliximab-dyyb, infliximab-abda, infliximab-qbtx, and infliximab-axxq) not listed above are considered **investigational**, including, but not limited to:

- Age-related macular degeneration
- Alcoholic hepatitis
- Arthritis (other than rheumatoid arthritis and psoriatic arthritis)
- Behçet's syndrome
- Behçet's syndrome uveitis
- Cancer cachexia
- Depression
- Diabetic macular edema
- Endometriosis
- Erythrodermic or exfoliative psoriasis
- Giant cell arteritis
- Graft-versus-host disease (GVHD)
- Intra-articular injections
- Juvenile idiopathic arthritis (JIA)
- Juvenile idiopathic arthritis-associated uveitis
- Kawasaki disease
- Polyarteritis nodosa
- Polymyalgia rheumatica
- Renal cell carcinoma
- Sacroiliitis
- Sarcoidosis
- Sclerosing cholangitis
- Sjögren syndrome
- Systemic lupus erythematosus
- Systemic necrotizing vasculitides
- Systemic sclerosis
- Wegener's granulomatosis

Infliximab (Remicade®), infliximab-dyyb (Inflectra™), infliximab-abda (Renflexis™), infliximab-qbtx (Ixifi™), and infliximab-axxq (Avsola™) are considered **not** medically necessary when used in combination with other biologics such as Enbrel® (etanercept), Kineret® (anakinra), Orencia®

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(abatacept), Rituxan® (rituximab), Humira® (adalimumab), Cimzia® (certolizumab), Simponi® (golimumab), Kevzara® (sarilumab), Cosentyx® (secukinumab), Actemra® (tocilizumab), or Xeljanz® (tofacitinib).

The use of Ixifi™ (infliximab-qbtx) in children with ulcerative colitis is considered investigational.

Policy Guidelines

Initial treatment is typically administered in a three-dose induction regimen. 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 typically given every 6 - 8 weeks.

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

- **Rheumatoid arthritis:** Max 10mg/kg every 4 weeks; allow 3-5 mg/kg at 0, 2, 6 weeks as part of initial therapy only, then every 8 weeks thereafter.
- **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, then every 8 weeks thereafter.
- **Ulcerative colitis:** For adults and pediatric patients ages 6 years and older: Max 5 mg/kg every 8 weeks; allow 5mg/kg at 0, 2, 6 weeks as part of initial therapy only, then every 8 weeks thereafter.
- **Ankylosing spondylitis:** Max 5mg/kg every 6 weeks; allow 5mg/kg at 0, 2, 6 weeks as part of initial therapy only, then every 6 weeks thereafter.
- **Psoriatic arthritis:** Max 5mg/kg every 8 weeks; allow 5mg/kg at 0, 2, 6 weeks as part of initial therapy only, then every 8 weeks thereafter.
- **Plaque psoriasis:** Max 5mg/kg every 8 weeks; allow 5mg/kg at 0, 2, 6 weeks as part of initial therapy only, then every 8 weeks thereafter.

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

Ixifi™ has not been studied in children with ulcerative colitis < 6 years of age.

Infliximab is particularly effective in the management of immune-related colitis, according to the National Comprehensive Cancer Network (NCCN) Guidelines. For patients with severe immune-related adverse events who are not responsive to steroids within 2 to 3 days, early initiation of TNF-alpha blocker therapy (i.e. infliximab 5 mg/kg) may be warranted in consultation with a relevant medical specialist. While duration of therapy with TNF-alpha blockers (infliximab) is not clearly defined, treatment for this indication is typically administered as a single dose. However, a second dose may be required in certain instances of no improvement, and can be administered 14 days after the initial dose.

Patients with refractory moderate to severe hidradenitis suppurativa show treatment benefit with biologics, such as adalimumab (Humira) and infliximab. Although adalimumab is the only FDA approved biologic treatment for hidradenitis suppurative, infliximab has demonstrated efficacy data in support of its use in the management of this indication. In a randomized, double-blind, placebo-controlled crossover trial of 38 patients with moderate to severe hidradenitis suppurativa, patients received initial infusions with either infliximab (5 mg/kg on weeks 0, 2, and 6) or placebo. The initial phase was followed by an open-label phase in which patients in the infliximab group received maintenance doses of infliximab at weeks 14 and 22, and patients in the placebo group were given the option to receive infliximab based on the same treatment regimen. There was no significant difference between treatment and placebo groups for the primary outcome at week 8 ($\geq 50\%$ decrease in an unvalidated disease severity score); however, infliximab demonstrated a statistically significant improvement in patient quality of life, pain, and physician global assessment scores. According to

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current North American hidradenitis suppurativa guidelines, expert experience suggests that titration to doses of 10 mg/kg every 4 to 8 weeks may be needed for ideal management of disease.

Infliximab Site of Care Eligibility

1. Infliximab administration may be given in an inpatient setting if the inpatient setting is medically necessary. An inpatient admission for the sole purpose of Infliximab infusion is not medically necessary, OR
2. Infliximab administration in a hospital outpatient setting is considered medically necessary if the following criteria are met:
 - a. History of mild adverse events that have not been successfully managed through mild pre-medication (diphenhydramine, acetaminophen, steroids, fluids, etc.), OR
 - b. Inability to physically and cognitively adhere to the treatment schedule and regimen complexity, OR
 - c. First infusion, OR
 - d. Less than 3 months since first Infliximab infusion, OR
 - e. First infusion after six months of no Infliximab infusions, OR
 - f. Requirement of a change in Infliximab product.
3. Members who do not meet the criteria above are appropriate for Infliximab administration in a **home-based infusion** or physician office setting with or without supervision by a certified healthcare professional. Inpatient and hospital outpatient infusion, in the absence of the criteria in #1 or #2 above is considered not medically necessary.

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: C9399, J1745, J3490, J3590, E0691- E0694, Q5103, Q5104, Q5109

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

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

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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>

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.15, 12/8/2011

Specialty Matched Consultant Advisory Panel Review 2/2012

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.15, 9/13/12

Specialty Matched Consultant Advisory Panel Review 2/2013

US Food and Drug Administration (FDA). Remicade (infliximab). Prescribing Information-March 2013 Update. Available online at: <http://www.fda.gov/safety/medwatch/safetyinformation/ucm247032.htm>. Last accessed September 2013.

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.15, 10/10/13

US Food and Drug Administration (FDA). Remicade (infliximab). Prescribing Information-March 2013 Update. Available online at: <http://www.fda.gov/safety/medwatch/safetyinformation/ucm247032.htm>. Last accessed March 2014.

Specialty Matched Consultant Advisory Panel Review 2/2014

Sr. Medical Director review 6/2014

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.15, 10/9/14

Specialty Matched Consultant Advisory Panel Review 2/2015

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.15, 11/12/15

US Food and Drug Administration (FDA). INFLECTRA (infliximab-dyyb). Prescribing information-April 2016. Available online at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125544s000lbl.pdf

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.15, 10/13/16

Infliximab (Remicade®) and Infliximab Biosimilars

US Food and Drug Administration (FDA). RENFLEXIS (infliximab-abda). Prescribing information-April 2017. Available online at:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761054Orig1s000lbl.pdf

Specialty Matched Consultant Advisory Panel Review 2/2018

US Food and Drug Administration (FDA). Remicade (infliximab). Prescribing Information-October 2017 Update. Available online at:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/103772s5377lbl.pdf. Last accessed March 2018.

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.15, 10/12/17

Medical Director review 3/2018

Medical Director review 7/2018

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.15, 10/10/18

US Food and Drug Administration (FDA). Ixifi (infliximab-qbtx). Prescribing Information-December 2017 Update. Available online at:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761072s000lbl.pdf. Last accessed December 2018.

Specialty Matched Consultant Advisory Panel Review 2/2019

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Management of Immunotherapy-Related Toxicities, version 2.2019. Revised April 8, 2019.

Available at: https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf. Accessed April 2019.

Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. *N Engl J Med*. 2018 Jan 11;378(2):158-168.

Medical Director review 4/2019

Medical Director review 9/2019

Grant A, Gonzalez T, Montgomery MO, et al. Infliximab therapy for patients with moderate to severe hidradenitis suppurativa: a randomized, double-blind, placebo-controlled crossover trial. *J Am Acad Dermatol*. 2010 Feb;62(2):205-17.

Blok JL, van Hattem S, Jonkman MF, et al. Systemic therapy with immunosuppressive agents and retinoids in hidradenitis suppurativa: a systematic review. *Br J Dermatol*. 2013 Feb;168(2):243-52.

Alikhan A, Sayed C, Alavi A, et al. North American clinical management guidelines for hidradenitis suppurativa: a publication from the United States and Canadian Hidradenitis Suppurativa Foundations. Part II: Topical, intralesional, and systemic medical management. *J Am Acad Dermatol* 2019 Jul;81(1):91-101.

Medical Director review 10/2019

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.15, 10/17/19

Amgen Inc. Avsola (infliximab-axxq) for injection for intravenous use. Highlights of prescribing information. December 2019. Available at: https://www.pi.amgen.com/~media/amgen/repositorysites/pi-amgen-com/avsola/avsola_pi_english.ashx. Last accessed January 2020.

Infliximab (Remicade®) and Infliximab Biosimilars

Celltrion, Inc. and Pfizer Labs. Inflectra (infliximab-dyyb) for injection for intravenous use. Highlights of prescribing information. June 2019. Available at: <http://labeling.pfizer.com/ShowLabeling.aspx?format=PDF&id=9271>. Last accessed January 2020.

Merck & Co., Inc. Renflexis (infliximab-abda) for injection for intravenous use. Highlights of prescribing information. October 2019. Available at: http://www.merck.com/product/usa/pi_circulars/r/renflexis/renflexis_pi.pdf. Last accessed January 2020.

Medical Director review 2/2020

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Policy Implementation/Update Information

For Policy Titled: "Infliximab (Remicade)"

- 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; 1.c. "as maintenance of remission in Crohn's disease". Changed language in 1.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 "1.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, 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.

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- 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)
- 3/20/12 Added FDA approved indication for pediatric patients ages 6 years or older for the treatment of ulcerative colitis. Added the following indications to the investigation status under "When Not Covered" for consistency with BCBSA: age-related macular degeneration, alcoholic hepatitis, depression, diabetic macular edema, erythrodermic or exfoliative psoriasis, systemic sclerosis, Wegener's granulomatosis, cancer cachexia, endometriosis, giant cell arteritis, intraarticular injections, Kawasaki syndrome, gonarthritis, polymyalgia rheumatic, renal cell carcinoma, sacroiliitis, sclerosing cholangitis, Sjogren syndrome, systemic necrotizing vasculitides. Specialty Matched Consultant Advisory Panel review 2/29/2012. No change to policy statement. (lpr)
- 3/12/13 Under "Not Covered" section, added Hidradenitis suppurativa as investigational indication. Reference added. Specialty Matched Consultant Advisory Panel review meeting 2/2013. (lpr)
- 7/30/13 Under "When Covered" section, added UVB therapy to statement 1.e. "as treatment of severe plaque type psoriasis (as evidenced by psoriatic plaques covering at least 10% of the body surface) that has failed prior treatment with psoralen-UVA, or UVB light therapy, or conventional systemic therapies (methotrexate, cyclosporine, Soriatane), or patient has contraindication to these treatments." Medical director review 6/2013. Added HCPCS codes E0691-E0694 to the Billing/Coding section. (lpr)
- 11/26/13 Reference updated. No change to policy statement. (lpr)

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- 4/1/14 Specialty Matched Consultant Advisory Panel review meeting 2/25/2014. Renumbered quantity limitations under Policy Guidelines section. Under “When Covered” section 1.g.: added neurosarcoid to diagnosis reference; under 2.contraindications list:added “any active infections” for c. and “demyelinating disease” for d. Under “When Not Covered” section added (JIA) juvenile idiopathic arthritis to (JRA) juvenile rheumatoid arthritis reference as these terms are synonymous. Medical director review. Policy noticed on 4/1/14 for effective date 6/10/14. (lpr)
- 7/15/14 Under “When Covered” section: changed **and** to **or** under 1.f. Under “When Not Covered” section: #23 Sarcoidosis-added “except neurosarcoidosis”. Reviewed by Sr.Medical Director. No change to policy statement. (lpr)
- 11/11/14 Reference added. No change to policy statement. (lpr)
- 3/10/15 Specialty Matched Consultant Advisory Panel review meeting 2/25/2015. No change to policy statement. (lpr)
- 4/1/16 Specialty Matched Consultant Advisory Panel review 2/24/2016. No change to policy. (an)
- 7/1/16 Added code Q5102 to Billing/Coding section. (an)

For Policy Re-titled: “Infliximab, Infliximab-dyyb”

- 12/30/16 Policy name changed from *Infliximab (Remicade)* to *Infliximab, Infliximab-dyyb*. Information added regarding Inflectra™ (infliximab-dyyb). Inflectra™ may be medically necessary when the criteria listed above for Remicade® is met **and** the patient has tried and failed, or is intolerant to, or has a clinical contraindication to Remicade®. References updated. (an)
- 3/31/17 Deleted several investigational indications from the Not Covered section. Specialty Matched Consultant Advisory Panel review 2/22/2017. (an)
- 8/25/17 Information regarding Renflexis (infliximab-abda), a biosimilar product, added to policy. (an)
- 12/29/17 Site of care criteria added to Policy Guidelines. Notification given 12/29/17 for policy effective date of 4/1/2018. (an)
- 1/26/18 Policy name “Nononcologic Uses of Rituximab” replaced with correct policy name “Rituximab for the Treatment of Rheumatoid Arthritis” in the Description section. Policy remains on notice for effective date 4/1/2018. (an)
- 3/29/18 Code Q5102 deleted from Billing/Coding Section. New codes Q5103, Q5104 effective 4/1/2018 added. (an)
- 4/13/18 Information added regarding Renflexis™ (infliximab-abda). Formatting under “When covered” #1 updated with specific headings for each disease state for clarity with no change to policy intent, and updated list of contraindications under #2 to include hypersensitivity and malignancy. Under “When not covered” and “Policy Guidelines” removed Crohn’s disease as investigational indication in children for Inflectra™ (infliximab-dyyb) and Renflexis™ (infliximab-abda), as this is a covered indication. Under “When not covered,” added “Cimzia® (certolizumab), Simponi® (golimumab), Kevzara® (sarilumab), Cosentyx® (secukinumab), Actemra® (tocilizumab), or Xeljanz® (tofacitinib)” to list of biologics. Minor edits made and typographical errors corrected throughout policy for clarity. References updated. Specialty Matched Consultant Advisory Panel review 2/28/2018. Medical Director review 4/2018. (krc)

For Policy Re-titled: “Infliximab, Infliximab-dyyb, Infliximab-abda”

Infliximab (Remicade®) and Infliximab Biosimilars

- 5/11/18 Policy name changed from *Infliximab, Infliximab-dyyb* to *Infliximab, Infliximab-dyyb, Infliximab-abda*. No change to policy intent. (krc)
- 7/13/18 Updated “When Covered” section for rheumatoid arthritis section to include the following statement: “or in combination with an alternative immunosuppressive agent if methotrexate is contraindicated or not tolerated.” Medical Director review 7/2018. (krc)
- 7/27/18 Updated “When Covered” section for rheumatoid arthritis to include the following statement: “or in combination with an alternative disease-modifying antirheumatic drug (e.g. leflunomide, sulfasalazine, hydroxychloroquine), if methotrexate is contraindicated or not tolerated.” Medical Director review 7/2018. (krc)

For Policy Re-titled: “Infliximab, Infliximab-dyyb, Infliximab-abda, Infliximab-qbtx”

- 12/31/18 Policy name changed from *Infliximab, Infliximab-dyyb, Infliximab-abda* to *Infliximab, Infliximab-dyyb, Infliximab-abda, Infliximab-qbtx*. Updated Description, Policy Guidelines, and Policy Statements to reflect approval of additional biosimilar to Remicade, Ixifi. Added HCPCS code Q5109 to Billing/Coding section effective 1/1/19. References added. (krc)
- 3/12/19 Specialty Matched Consultant Advisory Panel review 2/20/2019. No change to policy statement. (krc)
- 4/30/19 Under “When Covered,” added the indication “Immune Checkpoint Inhibitor-Related Gastrointestinal Toxicity” with the following criteria: “to treat moderate to severe diarrhea or colitis that develops during immune checkpoint inhibitor (PD-1, PD-L1) therapy, and stool evaluation has ruled out an infectious etiology, and the gastrointestinal symptoms are steroid-refractory.” Updated Policy Guidelines to reflect dosing guidelines for additional indication. References added. Medical Director review 4/2019. (krc)
- 10/1/19 Under “When Covered,” edited list of contraindications to only include moderate to severe heart failure and previous severe hypersensitivity reaction to infliximab as labeled contraindications. Medical Director review 9/2019. (krc)
- 10/29/19 Under “When Covered,” added the indication “Hidradenitis Suppurativa” with the following criteria: “to treat moderate to severe refractory hidradenitis suppurativa, and the patient has tried and failed, or is intolerant to, or has a clinical contraindication to adalimumab (Humira),” and removed “hidradenitis suppurativa” from “When Not Covered” section. Updated Policy Guidelines to reflect dosing and information for additional indication. References added. Medical Director review 10/2019. (krc)

For Policy Re-titled: “Infliximab (Remicade®) and Infliximab Biosimilars”

- 2/11/20 Policy name changed from *Infliximab, Infliximab-dyyb, Infliximab-abda, Infliximab-qbtx* to *Infliximab (Remicade®) and Infliximab Biosimilars*. Updated Description, Policy Guidelines, and Policy Statements to reflect approval of additional biosimilar to Remicade: Avsola (infliximab-axxq), with the same FDA approved indications as Remicade (parent drug). For Inflectra and Renflexis, removed “with the exception of ulcerative colitis in pediatric patients” under “When Covered” and removed pediatric ulcerative colitis as investigational in “When Not Covered.” Updated dosing recommendations within Policy Guidelines for clarity. Added HCPCS codes C9399, J3490, and J3590 to Billing/Coding section. References added. Medical Director review 2/2020. (krc)
- 3/10/20 Specialty Matched Consultant Advisory Panel review 2/19/2020. No change to policy statements. (krc)

Infliximab (Remicade®) and Infliximab Biosimilars

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