



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all health benefit plans administered by CIGNA Companies including plans formerly administered by Great-West Healthcare, which is now a part of CIGNA.

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Subject **Infliximab (Remicade®)**

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Hyperlink to Related Coverage Policies

Actemra®
 Cimzia®
 Enbrel®
 Humira®
 Kineret®
 Orencia®
 Rituxan®
 Simponi™

INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations. Proprietary information of CIGNA. Copyright ©2011 CIGNA

Coverage Policy

CIGNA covers infliximab (Remicade®) as medically necessary for treatment of ANY of the conditions listed when the associated criteria are met:

- used, in combination with methotrexate (MTX), for active rheumatoid arthritis (RA) in an adult for **EITHER** of the following indications:
 - history of a beneficial clinical response to infliximab
 - inadequate response, intolerance, or contraindication to at least one disease-modifying anti-rheumatic drugs (DMARDs) (i.e., MTX, Azathioprine, gold, Hydroxychloroquine, Leflunomide, Penicillamine, Sulfasalazine) **AND** to **TWO self administered preferred** tumor necrosis factor (TNF) antagonists [adalimumab (Humira®) and etanercept (Enbrel®)]
- polyarticular juvenile idiopathic arthritis (JIA) in a child 2 years of age and older for **EITHER** of the following indications:
 - history of a beneficial clinical response to infliximab
 - inadequate response, intolerance, or contraindication to at least one disease-modifying anti-rheumatic drugs (DMARDs) (i.e., Methotrexate (MTX) Azathioprine, gold, Hydroxychloroquine, Penicillamine, Sulfasalazine) **AND** to **ONE self administered**

preferred tumor necrosis factor (TNF) antagonist [adalimumab (Humira[®]) and etanercept (Enbrel[®])]

- active Crohn's disease in an adult **AND ANY** of the following:
 - history of beneficial clinical response to infliximab
 - failure, contraindication, intolerance, or inadequate response to conventional therapies (i.e. aminosalicylate, corticosteroids, or immunomodulators) **AND** failure or intolerance to Humira
- active Crohn's disease in a child **AND ANY** of the following:
 - history of beneficial clinical response to infliximab
 - failure, contraindication, intolerance, or inadequate response to conventional therapies (i.e. aminosalicylate, corticosteroids, or immunomodulators)
- fistulizing Crohn's disease with fistula present over at least three months in duration
- ankylosing spondylitis **AND EITHER** of the following:
 - history of beneficial clinical response to infliximab
 - failure, contraindication, or intolerance to nonsteroidal anti-inflammatory drugs (NSAIDs) **AND to ONE preferred self-administered** tumor necrosis factor (TNF) antagonist [adalimumab (Humira[®]) OR etanercept (Enbrel[®])]
- psoriatic arthritis **OR** reactive arthritis **AND EITHER** of the following:
 - history of beneficial clinical response to infliximab
 - failure, contraindication, or intolerance to methotrexate therapy **AND to ONE preferred self-administered** tumor necrosis factor (TNF) antagonist [adalimumab (Humira[®]) OR etanercept (Enbrel[®])]
- chronic plaque psoriasis in an individual **AND EITHER** the following:
 - history of a beneficial clinical response to infliximab
 - history of an inadequate response or intolerance to **ONE preferred self-administered** tumor necrosis factor (TNF) antagonist [adalimumab (Humira[®]) OR etanercept (Enbrel[®])]
- ulcerative colitis (UC) **AND EITHER** of the following:
 - history of beneficial clinical response to infliximab
 - failure, inadequate response, contraindication or intolerance to conventional therapies: corticosteroids (e.g., prednisone, methylprednisolone), 5-aminosalicylic acid agents (e.g., sulfasalazine, mesalamine, balsalazide), immunosuppressants (e.g., azathioprine, cyclosporine, 6-mercaptopurine)
- inflammatory bowel disease arthritis **AND EITHER** of the following:
 - history of beneficial clinical response to infliximab
 - failure, contraindication, or intolerance to sulfasalazine, azathioprine, steroids, or, methotrexate

The dosage, frequency, site of administration, and duration of therapy are reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to infliximab (Remicade[®]) therapy.

FDA Approved Indications

Crohn's Disease

Remicade is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult and pediatric patients with moderately to severely active Crohn's disease 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 Crohn's disease.

Ulcerative Colitis

Remicade is indicated for reducing signs and symptoms, inducing and maintaining 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.

Rheumatoid Arthritis (RA)

Remicade, in combination with methotrexate, is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis.

Ankylosing Spondylitis

Remicade is indicated for reducing signs and symptoms in patients with active ankylosing spondylitis.

Psoriatic Arthritis

Remicade is indicated for reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in patients with psoriatic arthritis.

Plaque Psoriasis

Remicade is indicated for the treatment of adult 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.

FDA Recommended Dosing

Crohn's Disease or Fistulizing Crohn's Disease

The recommended dose of Remicade is 5 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter for the treatment of adults with moderately to severely active Crohn's disease or fistulizing Crohn's disease. 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.

The recommended dose of Remicade for children with moderately to severely active Crohn's disease is 5 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks.

Ulcerative Colitis

The recommended dose of Remicade is 5 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter for the treatment of moderately to severely active ulcerative colitis.

Rheumatoid Arthritis

The recommended dose of Remicade is 3 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 3 mg/kg every 8 weeks thereafter for the treatment of moderately to severely active rheumatoid arthritis. Remicade should be given in combination with methotrexate. 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.

Ankylosing Spondylitis

The recommended dose of Remicade is 5 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 6 weeks thereafter for the treatment of active ankylosing spondylitis.

Psoriatic Arthritis

The recommended dose of Remicade is 5 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter for the treatment of psoriatic arthritis. Remicade can be used with or without methotrexate.

Plaque Psoriasis

The recommended dose of Remicade is 5 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter for the treatment of chronic severe (i.e., extensive and/or disabling) plaque psoriasis.

Psoriasis/Reactive Arthritis/Inflammatory Bowel Disease

The recommended dose of infliximab is 5 mg/kg given as an intravenous infusion followed with additional similar doses at two and six weeks after the first infusion, then every eight weeks thereafter.

Drug Availability

Remicade IV injection is supplied in individually-boxed single-use vials in 100 mg infliximab in a 20 mL vial.

General Background

Pharmacology

Infliximab is a chimeric monoclonal antibody that binds specifically to human tumor necrosis factor alpha (TNF α). It neutralizes the biological activity of TNF α by binding with high affinity to the soluble and transmembrane forms of TNF α and inhibits binding of TNF α with its receptors.

Guidelines

American College of Rheumatology (ACR)

The American College of Rheumatology (ACR) 2010 recommendations include the use of nonbiologic and biologic therapies in patients with RA when starting or resuming these therapies. The 2010 ACR recommendations address five key areas including: the indications for use, monitoring for side-effects, screening for tuberculosis which is a risk factor associated with biologic DMARDs, and off-label uses. The duration of RA disease duration, disease severity, and prognostic features were also considered when developing these recommendations. According to ACR guideline, it is important that RA patients be seen regularly to assess disease activity, evaluate disease severity, and determine whether alternative therapies are warranted. Because there was no evidence to support a specific recommendation on the frequency of provider visits, a specific and potentially arbitrary time frame is not recommended at this point. However, based on these recommendations, commonly used but not exclusive tools to assess the RA disease activity include: Disease Activity Score (DAS) in 28 joints, Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), Rheumatoid Arthritis Disease Activity Index, Patient Activity Scale (PAS), and Routine Assessment Patient Index Data. In addition it is recommended to use the combinations of commonly used but not exclusive prognostic factors to evaluate the patients with RA, including: Health Assessment Questionnaire (HAQ) score, Evidence of radiographic erosions, Elevated erythrocyte sedimentation rate, Elevated C-reactive protein level, and elevated levels of rheumatoid factor (RF) and/or anti-cyclic citrullinated peptide (anti-CCP) antibodies. Due to the absence of a single "gold standard" measure, multiple measures or pooled indices are used to determine a diagnosis, estimate prognosis, and to assess and monitor disease activity and response to treatment. Other commonly used measures in the clinical settings include: Visual Analogue scale (VAS), Likert scales of global response to pain by the patient/doctor, and Global Arthritis Score (GAS).

Many autoimmune rheumatic diseases have severe multisystem manifestations, including internal organ involvement and premature death. Unfortunately, for many of these conditions, standard (FDA approved) therapies do not exist, or are only effective in a subset of patients. The rarity of some of these conditions presents a barrier to performing large scale studies required for regulatory approval. However, valuable information is obtained in the published clinical reports of biologic DMARD therapies for many less common but disabling autoimmune conditions. When successful treatment options have been clearly documented in peer-reviewed journals, patients should receive the opportunity to benefit from these effective therapies.

While the American College of Rheumatology (ACR) offers a model for recommended off-label coverage criteria for use of TNF's. Other uses where TNF products have shown efficacy of use have not been shown with this

product. Therefore, any other use for this product that is not listed in the criteria coverage stem is considered experimental, investigational, and unproven.

American Academy of Dermatology (AAD)

The American Academy of Dermatology (AAD) published a consensus statement (Callen, et al., 2003) on psoriasis therapies. The document is intended to be used as a guide to the evaluation and treatments of psoriasis until evidence based guidelines are developed. Within this document, the authors state that BSA should not generally be used to determine which therapy to select; moderate and severe disease overlap and individuals with limited disease can be considered moderate for the purposes of selecting a therapy. Topical therapies are recommended for limited plaque disease. For moderate to severe disease, the AAD recommends phototherapy, targeted phototherapy, narrowband UVB, photochemotherapy with psoralen and UVA light (PUVA), topicals and systemic treatments.

Clinical Efficacy

Off Label Covered Indications

Polyarticular Juvenile Idiopathic Arthritis (JIA)

A randomized, controlled clinical study found favorable results for infliximab in polyarticular JIA (Ruperto, et al., 2007). 122 children with persistent polyarticular JIA despite prior methotrexate therapy were randomized to receive infliximab or placebo for 14 weeks, after which all children received infliximab through week 44. Patients received methotrexate plus infliximab 3 mg/kg through week 44, or methotrexate plus placebo for 14 weeks followed by MTX plus infliximab 6 mg/kg through week 44. The investigators reported that a higher proportion of patients in the 3 mg/kg infliximab group than in the placebo group had achieved responses according to the ACR Pediatric 30 (Pedi 30) criteria for improvement at week 14 (63.8% and 49.2%, respectively), but the between-group difference in this primary efficacy end point was not statistically significant ($p = 0.12$). The investigators reported that, by week 16, after the crossover from placebo to infliximab 6 mg/kg when all patients were receiving infliximab, an ACR Pedi 30 response was achieved in 73.2% of all patients. By week 52, ACR Pedi 50 and ACR Pedi 70 responses had been reached in 69.6% and 51.8%, respectively, of patients.

An open-label extension of this study of JIA concluded that infliximab was safe and effective in the long-term, but had a high discontinuation rate (Ruperto, et al., 2010). 78 of the 122 subjects from the 2007 study entered this extension study. The authors reported that infliximab at a mean dose of 4.4 mg/kg per infusion was generally well tolerated. Infusion reactions occurred in 32% (25/78) of patients, with a higher incidence in patients positive for antibodies to infliximab (58%, 15/26). At four years, the proportions of patients achieving ACR-Pedi-30/50/70/90 response criteria and inactive disease status were 44%, 40%, 33%, 24%, and 13%, respectively.

Ongoing Studies

Remicade is being studied for use in uveitis. At this time, however, there is insufficient published data in terms of safety and efficacy to support the use of Remicade for this indication.

A prospective trial completed in 2009 showed benefit for the use of Remicade in uveitis (Suhler, 2009). Ardoin (2007) and Sobrin (2007) offered a retrospective case series and a retrospective review, respectively, which showed positive results with low incidence of adverse events. Although the results of these reviews and the prospective trial were positive, further studies of well-controlled randomized trials are required to support Remicade's safety and efficacy for off label use in uveitis.

Adverse Reactions

Tuberculosis (TB), invasive fungal infections, and other opportunistic infections have been observed in patients receiving infliximab. Many of the serious infections have occurred in patients on concomitant immunosuppressive therapy that, in addition to their disease, could predispose them to infections. Infliximab should not be given to patients with a clinically important, active infection. In addition, cases of leukopenia, neutropenia, thrombocytopenia, and pancytopenia, some fatal, have been reported. In clinical trials of all TNF inhibitors, more cases of lymphoma were observed compared with controls and the expected rate in the general population. However, patients with rheumatoid arthritis and Crohn's disease may be at higher risk for developing lymphoma. In clinical trials of some TNF inhibitors, including infliximab, more cases of other malignancies were observed compared with controls.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:

HCPCS Codes	Description
J1745	Injection, infliximab, 10 mg

ICD-9-CM Diagnosis Codes	Description
555.0-555.9	Regional enteritis (Crohn's disease, inflammatory bowel disease)
556.0-556.9	Ulcerative colitis
696.0	Psoriatic arthropathy
696.1	Other psoriasis
696.2	Parapsoriasis
714.0-714.2	Rheumatoid arthritis
714.30	Polyarticular juvenile rheumatoid arthritis, chronic or unspecified
720.0	Ankylosing spondylitis

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Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare Great-West Healthcare	7/15/2008	5112	Infliximab (Remicade®)

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