

Subject: Infliximab (Remicade™)	
<input type="checkbox"/> Original	Original Committee Approval: October 13, 2006
<input checked="" type="checkbox"/> Revised	Last Committee Approval: December 3, 2008
	Last Review: October 19, 2007

1. Background:

Infliximab is a genetically engineered chimeric murine/human monoclonal antibody specifically directed against tumor necrosis factor-alpha (TNF-alpha). Its binding of both soluble and transmembrane TNF-alpha inhibits TNF-alpha's interaction with its receptors, reducing its biologic activity.¹ Tumor necrosis factor (TNF) is a cytokine produced by macrophages and T-cells. Research has revealed that TNF has a broad spectrum of biologic functionality. In particular, it is a key mediator of inflammation and is produced in response to infection and immunologic injury. Elevated concentrations of TNF-alpha have been found in the joints of rheumatoid arthritis patients and in the stools of Crohn's disease patients and have been correlated with increased disease activity.

Infliximab received FDA approval in August 1998 for the treatment of moderately to severely active Crohn's disease in patients with an inadequate response to conventional therapies, and treatment of patients with fistulizing Crohn's disease for the reduction in the number of draining enterocutaneous fistula(s). Since that time, supplemental Biologics License Applications have been approved for infliximab for the following additional uses:²

- Moderately to severely active rheumatoid arthritis in combination with methotrexate,
- Reducing the signs and symptoms of active arthritis in patients with psoriatic arthritis,
- Moderate to severe ulcerative colitis in patients who have not responded well to other therapy,
- Moderate to severe plaque psoriasis in patients who have not responded well to other therapy, and
- Reducing the signs and symptoms of active ankylosing spondylitis.

Infliximab is administered parenterally; therefore, it is not covered under retail pharmacy benefits.

2. Indications/Criteria:

The use of infliximab may be considered medically necessary for its labeled indications of:

Crohn's

Fistulizing Crohn's disease or inducing and maintaining clinical remission in patients with moderately to severely active Crohn's disease in patients with an inadequate response or intolerance to conventional therapy: Conventional therapy, for the purpose of this policy, includes the use of 3 or more of the following:

- corticosteroids (e.g., prednisone, prednisolone, dexamethasone, budesonide),
- sulfasalazine,
- immunomodulatory drugs (e.g., azathioprine, mercaptopurine, cyclosporine, methotrexate),
- 5-aminosalicylic acid (brand names include Rowasa[®], Pentasa[®] and Asacol[®]) and
- antibiotics (e.g., metronidazole, quinolones).

Colitis

Moderately to severely active ulcerative colitis in patients who have had an inadequate response to conventional therapy: Conventional therapy, for the purpose of this policy, includes the use of the following:

- topical and oral aminosalicylates,
- topical, oral or IV corticosteroids,
- oral or IV immunotherapy (e.g., azathioprine, 6-mercaptopurine, cyclosporine) and
- surgery for refractory disease.

Rheumatoid Arthritis

Moderately- to severely-active rheumatoid arthritis when used in combination with methotrexate AND history of an adequate (•12 week) trial and therapeutic failure or intolerance with at least one formulary (preferred) TNF-alpha inhibitor (etanercept or adalimumab).

Psoriatic Arthritis

Active psoriatic arthritis AND history of an adequate (•12 week) trial and therapeutic failure or intolerance with at least one formulary (preferred) TNF-alpha inhibitor (etanercept or adalimumab).

Ankylosing Spondylitis

Active ankylosing spondylitis refractory to conventional therapy AND history of an adequate (•12 week) trial and therapeutic failure or intolerance with at least one formulary (preferred) TNF-alpha inhibitor (etanercept or adalimumab).

Conventional therapy, for the purpose of this policy, includes the use of at least 3 of the following:

- nonsteroidal anti-inflammatory drugs (NSAIDs),

- immunomodulatory agents (e.g., methotrexate, azathioprine, mercaptopurine, cyclosporine),
- local steroid injections or
- sulfasalazine.

Plaque psoriasis

Chronic moderate to severe plaque psoriasis (psoriasis vulgaris) AND meeting all the following additional criteria:

- Involvement of •10% of the patient's body surface area (BSA). Exceptions may be considered for extensive recalcitrant facial involvement, pustular involvement of the hands or feet, and/or genital involvement interfering with normal sexual function,
- History of an adequate trial and treatment failure with phototherapy or photochemotherapy or such treatment is contraindicated, not tolerated, or unavailable,
- History of an adequate trial and treatment failure with •1 approved systemic therapy (e.g., methotrexate) or such treatment is contraindicated or not tolerated, and
- History of an adequate (• 12 week) trial and therapeutic failure or intolerance with at least one formulary (preferred) TNF-alpha inhibitor (etanercept or adalimumab).

Note:

For **all** of the above indications, CHP will approve use of Remicade if there is documented evidence of previous and ongoing (current) favorable response to this drug.

3. Authorization guidelines:

1. Crohn's disease:

- Initial therapy with up to 5 infusions in a 6-month period when the criteria listed above are met. The 5 infusions include the recommended loading dose of 5 mg/kg at weeks 0, 2, and 6, plus a maintenance infusion every 8 weeks.
- Retreatment may be approved at a maximum of 6 infusions in a 12-month time period based on the following criteria:
 - Patient met initial coverage criteria listed above,
 - A significant/sustained response to the last infliximab course is documented in the patient's progress notes, and
 - History that either azathioprine or mercaptopurine was not effective at maintaining remission, use of these agents was contraindicated, or they were not tolerated.
- For patients who respond and then lose their response, adjusting the dosing frequency to as often as every 4 weeks or increasing the dose to 10 mg/kg, but not both concurrently, may be approved.

2. Ulcerative colitis:

- Initial therapy with up to 5 infusions in a 6-month period may be approved when the criteria listed above are met. The 5 infusions include the recommended loading dose of 5 mg/kg at weeks 0, 2, and 6, plus a maintenance infusion every 8 weeks.
 - Retreatment may be approved at a maximum of 6 infusions in a 12-month time period based on the following criteria:
 - a) Patient met initial coverage criteria listed above, and
 - b) A significant/sustained response to the last infliximab course is documented in the patient progress notes.
3. Rheumatoid Arthritis:
- Initial therapy with up to 5 infusions of 3 mg/kg infliximab in a 6-month period, in combination with methotrexate, may be approved. The 5 infusions include the recommended loading doses at weeks 0, 2, and 6, plus an infusion every 8 weeks for maintenance.
 - Retreatment with infliximab may be approved at a maximum of 6 infusions in a 12-month time period based on the following criteria:
 - a) * An improvement in any 1 of the following American College of Rheumatology assessment components for improvement:
 - painful joint count,
 - swollen joint count,
 - patient pain assessment,
 - patient global assessment,
 - physician global assessment,
 - patient self-assessed disability, or
 - acute phase reactants (ESR or CRP).
 - b) For patients with an incomplete response, adjusting the dosing frequency to as often as every 4 weeks or increasing the dose to a maximum of 10 mg/kg, but not both concurrently, may be approved.
4. Psoriatic Arthritis:
- Initial therapy with up to 5 infusions in a 6-month period may be approved when the criteria listed above are met. The 5 infusions include the recommended loading dose of 5 mg/kg at weeks 0, 2, and 6, plus a maintenance infusion every 8 weeks.
 - Retreatment may be approved at a maximum of 6 infusions in a 12-month time period based on the following criteria:
 - a) Patient met initial coverage criteria listed above, and
 - b) A significant/sustained response to the last infliximab course is documented in the patient progress notes.
5. Ankylosing Spondylitis:
- Recommended dosing of infliximab for this indication includes an initial load of three IV infusions at 5 mg/kg over a 6-week timeframe (weeks 0, 2 and 6). Coverage of

retreatment (single 5 mg/kg doses every 6 weeks or more as needed) will require documentation of maintenance or improvement in disease severity before the first retreatment, and every six months thereafter.

- Baseline disease severity indices should be submitted so that treatment efficacy can be evaluated after the initial course. Such indices may include tender and swollen joint counts, patient global assessment, physician global assessment, patient pain assessment, levels of acute phase reactants (e.g., ESR, CRP), BASDAI score or ASAS response.
6. Plaque Psoriasis:
- Initial therapy with up to 5 infusions of 5 mg/kg of infliximab in a 6-month period may be approved. The 5 infusions include the recommended loading doses at weeks 0, 2, and 6, plus a maintenance infusion every 8 weeks. No additional benefit was observed for a dose of 10 mg/kg.
 - Retreatment with infliximab may be approved at a maximum of 6 infusions in a 12-month time period based on objective documentation of effectiveness.
7. General:
- Retreatment should be terminated if the patient develops symptoms of antibody reaction, such as myalgias, rash, fever and polyarthralgia, which have been reported to occur 2 or more years after the initial infusion in patients who continue to receive retreatment.
 - Patients not responding to therapy after 14 weeks are unlikely to respond, and consideration should be given to discontinuing infliximab therapy.
 - The use of infliximab may be considered investigational for the treatment of patients with:
 - a) Sarcoidosis,
 - b) Graft vs Host Disease,
 - c) Sjögren’s Syndrome,
 - d) Uveitis, or
 - e) Other pathological indications and/or arthropathies.

4. Limitations/Exclusions:

Healthy Options:	None; pre-authorization required.
Basic Health Plan:	None; pre-authorization required.
GAU:	None; pre-authorization required.
Medicare Advantage:	None; pre-authorization required.

5. Required Review and Approvals:

Infliximab (Remicade®) infusions require prior authorization by the CHP Medical Director or his/her designee. Initial authorization period will be for six months. Subsequent re-authorization periods will be as specified above.

¹ Centocor, Inc. Remicade® (infliximab recombinant) prescribing information. Centocor, Inc; 2005 Sep.

² US Food and Drug Administration Center for Drug Evaluation and Research. Infliximab Approval History. [Online]. [cited 2006 May 18]. Available from:

URL:http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#applist.