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Infliximab and Associated Biosimilars

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Related Policies (if applicable)
THE801.028 Acne Management

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: New Mexico: For plans delivered, or issued for delivery or renewal on or after January 1, 2025, NMSA 1978 §59A-22B-8 (SB 135) prohibits step therapy requirements before authorizing coverage for medication approved by the U.S. Food and Drug Administration (FDA) that is prescribed for the treatment of an autoimmune disorder, cancer, or a substance use disorder, pursuant to a medical necessity determination, except in cases in which a biosimilar, interchangeable biologic or generic version is available. Any approved step therapy exception may be continued for no less than the duration of the therapeutic effect of the drug. This does not prevent a requirement of a member trying biosimilars, interchangeable biologics or generics of a prescription drug before providing coverage for the equivalent brand name prescription

drug. This applies to the following: fully insured group business; Individual and Family Market plans, both on- and off-exchange; the State's Medicaid Plan; and the mandatory coverage for IBAC plans (i.e., State of New Mexico, Public Schools Insurance Authority, Albuquerque Public Schools and the New Mexico Retiree Health Care Authority).

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

NOTE 1: This medical policy does **NOT** address oncologic indications. This medical policy **IS NOT TO BE USED** for oncologic indications. Refer to RX502.061 Oncology Medications for oncologic indications.

Continuation Therapy:
Continuation of Renflexis or Ixifi therapy **is considered medically necessary** for all members (including new members):

- Who are currently receiving the requested medication for an indication listed below; AND
- Who are experiencing benefit from therapy as evidenced by disease stability or disease improvement; AND
- When dosing is in accordance with an authoritative source.

Initial Therapy:
Avsola, Inflectra, Infliximab (unbranded), and Remicade are the preferred agents, and coverage will be provided contingent on the coverage criteria in this Medical Policy.

Coverage for non-preferred agents, including but not limited to Renflexis or Ixifi, will be provided contingent to the criteria in this section. For patients initiating therapy, the following criteria would apply prior to Renflexis or Ixifi use:

- Patient has tried and failed, experienced an adverse reaction, intolerance, or has a clinical contraindication to at least two of the following preferred medications – Avsola, Inflectra, Infliximab (unbranded), and Remicade; AND

- Physician attests that in their clinical opinion, the same intolerance, contraindications, lack of clinical efficacy, or adverse event would not be expected to occur with non-preferred agents;

OR

- The preferred drugs are experiencing documented drug shortages or recalls from a wholesaler, manufacturer, the ASHP (American Hospital of Health-System Pharmacist) Drug Shortage web page or the US Food and Drug Administration.

State specific Drug Criteria may apply.

Infliximab and infliximab biosimilars **may be considered medically necessary** according to U.S. Food and Drug Administration **labeled** indications as outlined in the table below.

DISEASE	CRITERIA
Ankylosing spondylitis (Adult)	For reducing signs and symptoms in adult patients with active disease.
Crohn's disease (Adult)	• For reducing signs and symptoms and inducing and maintaining clinical remission in adult patients (18 years or older) with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. • For reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing disease.
Crohn's disease (Pediatric)	For reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy.
Plaque psoriasis (Adult)	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.
Psoriatic arthritis (Adult)	For reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage of active arthritis, and improving physical function.
Rheumatoid arthritis (Adult)	When given in combination with methotrexate, for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis.
Ulcerative colitis (Adult)	For reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active ulcerative colitis who have had inadequate response to conventional therapy.

Ulcerative colitis (Pediatric)	For reducing the signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active ulcerative colitis who have had inadequate response to conventional therapy.

Infliximab and infliximab biosimilars **may be considered medically necessary** for the following **off-label** indications:

- Granulomatosis with polyangiitis, refractory, in combination with corticosteroids;
- Hidradenitis suppurativa (severe), refractory;
- Juvenile idiopathic arthritis (severe), refractory to other therapies;
- Rheumatoid arthritis, monotherapy for patients who cannot tolerate methotrexate;
- Sarcoidosis (severe), refractory;
- Still's disease, adult onset;
- Synovitis;
- Takayasu's disease, refractory; or
- Uveitis, refractory; adjunct.

NOTE 2: Infliximab and infliximab biosimilars shall not be used concurrently with other biologics used to treat the indications above. Please refer to the Description Section for a list of biological disease-modifying antirheumatic drugs (DMARDs).

All other uses of infliximab (Remicade® and Infliximab (unbranded)) and infliximab biosimilars (i.e., Renflexis, Inflectra, Ixifi, and Avsola) not specified above **are considered experimental, investigational and/or unproven.**

Policy Guidelines

None.

Description

Table 1. Biological Disease-Modifying Antirheumatic Drugs (DMARDs)
Biological disease-modifying antirheumatic drugs (DMARDs)

Generic Name	Brand Name
abatacept	Orencia
adalimumab	Humira
anakinra	Kineret
apremilast	Otezla
baricitinib	Olumiant
brodalumab	Siliq
certolizumab	Cimzia
etanercept	Enbrel

golimumab	Simponi/Simponi Aria
guselkumab	Tremfya
ixekizumab	Taltz
risankizumab-rzaa	Skyrizi
rituximab	Rituxan/Riabni/Ruxience/Truxima
sarilumab	Kevzara
secukinumab	Cosentyx
tildrakizumab-asmn	Ilumya
tocilizumab	Actemra
tofacitinib	Xeljanz
upadactinib	Rinvoq
ustekinumab	Stelara
vedolizumab	Entyvio

Infliximab is a tumor necrosis factor α (TNF-α) blocking agent approved by the U.S. Food and Drug Administration (FDA) for the treatment of rheumatoid arthritis, Crohn's disease, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, and ulcerative colitis. Infliximab is also being considered as an off-label treatment for many other conditions.

Background

Tumor necrosis factor (TNF) is a cytokine produced by macrophages and T cells. Its name is based on the original observation 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-α blocking agents. This medical policy focuses on the label and off-label uses of infliximab and associated biosimilars for various medical conditions and diagnoses.

Regulatory Status

The FDA has approved Infliximab for the following indications (1):

- Crohn's Disease (Aug 1998):
  - Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy.
  - Reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing disease.
- Rheumatoid Arthritis in combination with methotrexate (Nov 1999): Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active disease.
- Ankylosing Spondylitis (Dec 2004): Reducing signs and symptoms in patients with active disease.
- Psoriatic Arthritis (May 2005): Reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function.

- Ulcerative Colitis (Sept 2005): Reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy.
- Pediatric Crohn's Disease (May 2006): Reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients with moderately to severely active disease who have had an inadequate response to conventional therapy.
- Plaque Psoriasis (Sept 2006): 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.
- Pediatric Ulcerative Colitis (Sept 2011): Reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients with moderately to severely active disease who have had an inadequate response to conventional therapy.

Infliximab (unbranded) and the following infliximab biosimilars have been FDA approved for the same indications as Remicade (2-5):

- Infliximab-dyyb (Inflectra) (Apr 2016);
- Infliximab-abda (Renflexis) (Apr 2017);
- Infliximab-qbtx (Ixifi) (Dec 2017);
- Infliximab-axxq (Avsola) (Dec 2019).

Rationale

This policy is based on both the U.S. Food and Drug Administration (FDA) labeled indications for Infliximab through July 2023, along with multiple accepted off-label indications.

FDA Labeled Indications (6)

Adult Crohn's Disease

Active Crohn's Disease in Adults

The safety and efficacy of single and multiple doses of Infliximab were assessed in 2 randomized, double-blind, placebo-controlled clinical studies in 653 patients with moderate to severely active Crohn's disease [Crohn's Disease Activity Index (CDAI) ≥220 and ≤400] with an inadequate response to prior conventional therapies. Concomitant stable doses of aminosalicylates, corticosteroids and/or immunomodulatory agents were permitted and 92% of patients continued to receive at least one of these medications.

In the single-dose trial of 108 patients, 16% (4/25) of placebo patients achieved a clinical response (decrease in CDAI ≥70 points) at Week 4 vs. 81% (22/27) of patients receiving 5 mg/kg Infliximab ($p<0.001$, two-sided, Fisher's Exact test). Additionally, 4% (1/25) of placebo patients and 48% (13/27) of patients receiving 5 mg/kg Infliximab achieved clinical remission (CDAI <150) at Week 4.

In a multidose trial (ACCENT I [Study Crohn's I]), 545 patients received 5 mg/kg at Week 0 and were then randomized to one of three treatment groups; the placebo maintenance group received placebo at Weeks 2 and 6, and then every 8 weeks; the 5 mg/kg maintenance group received 5 mg/kg at Weeks 2 and 6, and then every 8 weeks; and the 10 mg/kg maintenance group received 5 mg/kg at Weeks 2 and 6, and then 10 mg/kg every 8 weeks. Patients in response at Week 2 were randomized and analyzed separately from those not in response at Week 2. Corticosteroid taper was permitted after Week 6.

At Week 2, 57% (311/545) of patients were in clinical response. At Week 30, a significantly greater proportion of these patients in the 5 mg/kg and 10 mg/kg maintenance groups achieved clinical remission compared to patients in the placebo maintenance group (Table 2).

Additionally, a significantly greater proportion of patients in the 5 mg/kg and 10 mg/kg Infliximab maintenance groups were in clinical remission and were able to discontinue corticosteroid use compared to patients in the placebo maintenance group at Week 54 (Table 2).

Table 2. Clinical Remission and Steroid Withdrawal in Adult Patients with CD (Study Crohn's I)

	Single 5-mg/kg Dose[a]	**Three-Dose Induction[b]**	
	Placebo Maintenance	**Infliximab Maintenance q8 weeks**	
		5 mg/kg	**10 mg/kg**
Week 30	25/102	41/104	48/105
Clinical remission	25%	39%	46%
P-value[c]		0.022	0.001
Week 54	6/54	14/56	18/53
Patients in remission able to discontinue corticosteroid use[d]	11%	25%	34%
P-value[c]		0.059	0.005

[a] Infliximab at Week 0.
[b] Infliximab 5 mg/kg administered at Weeks 0, 2 and 6.
[c] P-values represent pairwise comparisons to placebo.
[d] Of those receiving corticosteroids at baseline.

Patients in the Infliximab maintenance groups (5 mg/kg and 10 mg/kg) had a longer time to loss of response than patients in the placebo maintenance group. At Weeks 30 and 54, significant improvement from baseline was seen among the 5 mg/kg and 10 mg/kg Infliximab-treated groups compared to the placebo group in the disease-specific inflammatory bowel disease questionnaire (IBDQ), particularly the bowel and systemic components, and in the physical component summary score of the general health-related quality of life questionnaire SF-36.

In a subset of 78 patients who had mucosal ulceration at baseline and who participated in an endoscopic substudy, 13 of 43 patients in the Infliximab maintenance group had endoscopic

evidence of mucosal healing compared to 1 of 28 patients in the placebo group at Week 10. Of the Infliximab-treated patients showing mucosal healing at Week 10, 9 of 12 patients also showed mucosal healing at Week 54.

Patients who achieved a response and subsequently lost response were eligible to receive Infliximab on an episodic basis at a dose that was 5 mg/kg higher than the dose to which they were randomized. The majority of such patients responded to the higher dose. Among patients who were not in response at Week 2, 59% (92/157) of Infliximab maintenance patients responded by Week 14 compared to 51% (39/77) of placebo maintenance patients. Among patients who did not respond by Week 14, additional therapy did not result in significantly more responses.

Fistulizing Crohn's Disease in Adults
The safety and efficacy of Infliximab were assessed in 2 randomized, double-blind, placebo-controlled studies in patients with fistulizing Crohn's disease with fistula(s) that were of at least 3 months duration. Concurrent use of stable doses of corticosteroids, 5-aminosalicylates, antibiotics, methotrexate (MTX), 6-mercaptopurine (6-MP) and/or azathioprine (AZA) was permitted.

In the first trial, 94 patients received 3 doses of either placebo or Infliximab at Weeks 0, 2 and 6. Fistula response (≥50% reduction in number of enterocutaneous fistulas draining upon gentle compression on at least 2 consecutive visits without an increase in medication or surgery for Crohn's disease) was seen in 68% (21/31) of patients in the 5 mg/kg Infliximab group (P=0.002) and 56% (18/32) of patients in the 10 mg/kg Infliximab group (P=0.021) vs. 26% (8/31) of patients in the placebo arm. The median time to onset of response and median duration of response in Infliximab-treated patients was 2 and 12 weeks, respectively. Closure of all fistulas was achieved in 52% of Infliximab-treated patients compared with 13% of placebo-treated patients (P<0.001).

In the second trial (ACCENT II [Study Crohn's II]), patients who were enrolled had to have at least 1 draining enterocutaneous (perianal, abdominal) fistula. All patients received 5 mg/kg Infliximab at Weeks 0, 2 and 6. Patients were randomized to placebo or 5 mg/kg Infliximab maintenance at Week 14. Patients received maintenance doses at Week 14 and then every 8 weeks through Week 46. Patients who were in fistula response (fistula response was defined the same as in the first trial) at both Weeks 10 and 14 were randomized separately from those not in response. The primary endpoint was time from randomization to loss of response among those patients who were in fistula response.

Among the randomized patients (273 of the 296 initially enrolled), 87% had perianal fistulas and 14% had abdominal fistulas. Eight percent also had rectovaginal fistulas. Greater than 90% of the patients had received previous immunosuppressive and antibiotic therapy.

At Week 14, 65% (177/273) of patients were in fistula response. Patients randomized to Infliximab maintenance had a longer time to loss of fistula response compared to the placebo

maintenance group. At Week 54, 38% (33/87) of Infliximab-treated patients had no draining fistulas compared with 22% (20/90) of placebo-treated patients (P=0.02). Compared to placebo maintenance, patients on Infliximab maintenance had a trend toward fewer hospitalizations.

Patients who achieved a fistula response and subsequently lost response were eligible to receive Infliximab maintenance therapy at a dose that was 5 mg/kg higher than the dose to which they were randomized. Of the placebo maintenance patients, 66% (25/38) responded to 5 mg/kg Infliximab, and 57% (12/21) of Infliximab maintenance patients responded to 10 mg/kg.

Patients who had not achieved a response by Week 14 were unlikely to respond to additional doses of Infliximab.

Similar proportions of patients in either group developed new fistulas (17% overall) and similar numbers developed abscesses (15% overall).

Pediatric Crohn's Disease

The safety and efficacy of Infliximab were assessed in a randomized, open-label study (Study Peds Crohn's) in 112 pediatric patients aged 6 to 17 years old with moderately to severely active Crohn's disease and an inadequate response to conventional therapies. The median age was 13 years, and the median Pediatric Crohn's Disease Activity Index (PCDAI) was 40 (on a scale of 0 to 100).

All patients were required to be on a stable dose of 6-MP, AZA, or MTX; 35% were also receiving corticosteroids at baseline. All patients received induction dosing of 5 mg/kg Infliximab at Weeks 0, 2, and 6. At Week 10, 103 patients were randomized to a maintenance regimen of 5 mg/kg Infliximab given either every 8 weeks or every 12 weeks.

At Week 10, 88% of patients were in clinical response (defined as a decrease from baseline in the PCDAI score of ≥15 points and total PCDAI score of ≤30 points), and 59% were in clinical remission (defined as PCDAI score of ≤10 points).

The proportion of pediatric patients achieving clinical response at Week 10 compared favorably with the proportion of adults achieving a clinical response in Study Crohn's I. The study definition of clinical response in Study Peds Crohn's was based on the PCDAI score, whereas the CDAI score was used in the adult Study Crohn's I.

At both Week 30 and Week 54, the proportion of patients in clinical response was greater in the every 8-week treatment group than in the every 12-week treatment group (73% vs. 47% at Week 30, and 64% vs. 33% at Week 54). At both Week 30 and Week 54, the proportion of patients in clinical remission was also greater in every 8-week treatment group than in the every 12-week treatment group (60% vs. 35% at Week 30, and 56% vs. 24% at Week 54), (Table 3).

For patients in Study Peds Crohn's receiving corticosteroids at baseline, the proportion of patients able to discontinue corticosteroids while in remission at Week 30 was 46% for every 8-week maintenance group and 33% for every 12-week maintenance group. At Week 54, the proportion of patients able to discontinue corticosteroids while in remission was 46% for every 8-week maintenance group and 17% for every 12-week maintenance group.

Table 3. Response and Remission in Study Peds Crohn's

	5 mg/kg Infliximab	
	Every 8 Week	**Every 12 Week**
	Treatment Group	**Treatment Group**
Patients Randomized	52	51
Clinical Response[a]		
Week 30	73%[d]	47%
Week 54	64%[d]	33%
Clinical Remission[b]		
Week 30	60%[c]	35%
Week 54	56%[d]	24%

[a] Defined as a decrease from baseline in the PCDAI score of ≥15 points and total score of ≤30 points.
[b] Defined as a PCDAI score of ≤10 points.
[c] P-value <0.05.
[d] P-value <0.01.

Adult Ulcerative Colitis

The safety and efficacy of Infliximab were assessed in 2 randomized, double-blind, placebo-controlled clinical studies in 728 patients with moderately to severely active ulcerative colitis (UC) (Mayo score 5-6 to 12 [of possible range 0 to 12], Endoscopy subscore ≥2) with an inadequate response to conventional oral therapies (Studies UC I and UC II). Concomitant treatment with stable doses of aminosalicylates, corticosteroids and/or immunomodulatory agents was permitted. Corticosteroid taper was permitted after Week 8. Patients were randomized at week 0 to receive either placebo, 5 mg/kg Infliximab or 10 mg/kg Infliximab at Weeks 0, 2, 6, and every 8 weeks thereafter through Week 46 in Study UC I, and at Weeks 0, 2, 6, and every 8 weeks thereafter through Week 22 in Study UC II. In Study UC II, patients were allowed to continue blinded therapy to Week 46 at the investigator's discretion. Patients in Study UC I had failed to respond or were intolerant to oral corticosteroids, 6-MP, or AZA.

Patients in Study UC II had failed to respond or were intolerant to the above treatments and/or aminosalicylates. Similar proportions of patients in Studies UC I and UC II were receiving corticosteroids (61% and 51%, respectively), 6-MP/AZA (49% and 43%) and aminosalicylates (70% and 75%) at baseline. More patients in Study UC II than UC I were taking solely aminosalicylates for UC (26% vs. 11%, respectively). Clinical response was defined as a decrease from baseline in the Mayo score by ≥30% and ≥3 points, accompanied by a decrease in the rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 or 1.

Clinical Response, Clinical Remission, and Mucosal Healing

In both Study UC I and Study UC II, greater percentages of patients in both Infliximab groups achieved clinical response, clinical remission and mucosal healing than in the placebo group. Each of these effects was maintained through the end of each trial (Week 54 in Study UC I, and Week 30 in Study UC II). In addition, a greater proportion of patients in Infliximab groups demonstrated sustained response and sustained remission than in the placebo groups (Table 4).

Of patients on corticosteroids at baseline, greater proportions of patients in the Infliximab treatment groups were in clinical remission and able to discontinue corticosteroids at Week 30 compared with the patients in the placebo treatment groups (22% in Infliximab treatment groups vs. 10% in placebo group in Study UC I; 23% in Infliximab treatment groups vs. 3% in placebo group in Study UC II). In Study UC I, this effect was maintained through Week 54 (21% in Infliximab treatment groups vs. 9% in placebo group). The Infliximab-associated response was generally similar in the 5 mg/kg and 10 mg/kg dose groups.

Table 4. Response, Remission and Mucosal Healing in Adult Ulcerative Colitis Studies

	Study UC I			**Study UC II**		
	Placebo	**5 mg/kg Infliximab**	**10 mg/kg Infliximab**	**Placebo**	**5 mg/kg Infliximab**	**10 mg/kg Infliximab**
Patients randomized	121	121	122	123	121	120
Clinical Response[a, d]						
Week 8	37%	69%*	62%*	29%	65%*	69%*
Week 30	30%	52%*	51%**	26%	47%*	60%*
Week 54	20%	45%*	44%*	NA	NA	NA
Sustained Response[d]						
(Clinical response at both Weeks 8 and 30)	23%	49%*	46%*	15%	41%*	53%*
(Clinical response at Weeks 8, 30, and 54)	14%	39%*	37%*	NA	NA	NA
Clinical Remission[b, d]						
Week 8	15%	39%*	32%**	6%	34%*	28%*
Week 30	16%	34%**	37%*	11%	26%**	36%*
Week 54	17%	35%**	34%**	NA	NA	NA
Sustained Remission[d]						
(Clinical response at both Weeks 8 and 30)	8%	23%**	26%*	2%	15%*	23%*

(Clinical response at Weeks 8, 30, and 54)	7%	20%**	20%**	NA	NA	NA
Mucosal Healing[c, d]						
Week 8	34%	62%*	59%*	31%	60%*	62%*
Week 30	7%	50%*	49%*	30%	46%**	57%*
Week 54	18%	45%*	47%*	NA	NA	NA

*P <0.001, **P <0.01.

[a] Defined as a decrease from baseline in the Mayo score by ≥30% and ≥3 points, accompanied by a decrease in the rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 or 1. (The Mayo score consists of the sum of four subscores: stool frequency, rectal bleeding, physician's global assessment and endoscopy findings.)

[b] Defined as a Mayo score ≤2 points, no individual subscore >1.

[c] Defined as a 0 or 1 on the endoscopy subscore of the Mayo score.

[d] Patients who had a prohibited change in medication, had an ostomy or colectomy, or discontinued study infusions due to lack of efficacy are considered to not be in clinical response, clinical remission or mucosal healing from the time of the event onward.

The improvement with Infliximab was consistent across all Mayo subscores through Week 54 (Study UC I shown in Table 5; Study UC II through Week 30 was similar).

Table 5. Proportion of Patients in Study UC I with Mayo Subscores Indicating Inactive or Mild Disease Through Week 54

	Study UC I		
		Infliximab	
	Placebo	**5mg/kg**	**10 mg/kg**
	(n=121)	**(n=121)**	**(n=122)**
Stool frequency			
Baseline	17%	17%	10%
Week 8	35%	60%	58%
Week 30	35%	51%	53%
Week 54	31%	52%	51%
Rectal bleeding			
Baseline	54%	40%	48%
Week 8	74%	86%	80%
Week 30	65%	74%	71%
Week 54	62%	69%	67%
Physician's Global Assessment			
Baseline	4%	6%	3%
Week 8	44%	74%	64%
Week 30	36%	57%	55%
Week 54	26%	53%	53%
Endoscopy findings			

Baseline	0%	0%	0%
Week 8	34%	62%	59%
Week 30	26%	51%	52%
Week 54	21%	50%	51%

Pediatric Ulcerative Colitis

The safety and effectiveness of Infliximab for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients aged 6 years and older with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy are supported by evidence from adequate and well-controlled studies of Infliximab in adults. Additional safety and pharmacokinetic data were collected in an open-label pediatric UC trial in 60 pediatric patients aged 6 through 17 years (median age 14.5 years) with moderately to severely active ulcerative colitis (Mayo score of 6 to 12; Endoscopic subscore ≥2) and an inadequate response to conventional therapies. At baseline, the median Mayo score was 8, 53% of patients were receiving immunomodulator therapy (6-MP/AZA/MTX), and 62% of patients were receiving corticosteroids (median dose 0.5 mg/kg/day in prednisone equivalents). Discontinuation of immunomodulators and corticosteroid taper were permitted after Week 0.

All patients received induction dosing of 5 mg/kg Infliximab at Weeks 0, 2, and 6. Patients who did not respond to Infliximab at Week 8 received no further Infliximab and returned for safety follow-up. At Week 8, 45 patients were randomized to a maintenance regimen of 5 mg/kg Infliximab given either every 8 weeks through Week 46 or every 12 weeks through Week 42. Patients were allowed to change to a higher dose and/or more frequent administration schedule if they experienced loss of response.

Clinical response at Week 8 was defined as a decrease from baseline in the Mayo score by ≥30% and ≥3 points, including a decrease in the rectal bleeding subscore by ≥1 points or achievement of a rectal bleeding subscore of 0 or 1.

Clinical remission at Week 8 was measured by the Mayo score, defined as a Mayo score of ≤2 points with no individual subscore >1. Clinical remission was also assessed at Week 8 and Week 54 using the Pediatric Ulcerative Colitis Activity Index (PUCAI) score and was defined by a PUCAI score of <10 points.

Endoscopies were performed at baseline and at Week 8. A Mayo endoscopy subscore of 0 indicated normal or inactive disease and a subscore of 1 indicated mild disease (erythema, decreased vascular pattern, or mild friability).

Of the 60 patients treated, 44 were in clinical response at Week 8. Of 32 patients taking concomitant immunomodulators at baseline, 23 achieved clinical response at Week 8, compared to 21 of 28 of those not taking concomitant immunomodulators at baseline. At Week 8, 24 of 60 patients were in clinical remission as measured by the Mayo score and 17 of 51 patients were in remission as measured by the PUCAI score.

At Week 54, 8 of 21 patients in the every 8-week maintenance group and 4 of 22 patients in the every 12-week maintenance group achieved remission as measured by the PUCAI score.

During maintenance phase, 23 of 45 randomized patients (9 in the every 8-week group and 14 in the every 12-week group) required an increase in their dose and/ or increase in frequency of Infliximab administration due to loss of response. Nine of the 23 patients who required a change in dose had achieved remission at Week 54. Seven of those patients received the 10 mg/kg every 8-week dosing.

Rheumatoid Arthritis

The safety and efficacy of Infliximab were assessed in 2 multicenter, randomized, double-blind, pivotal trials: ATTRACT (Study RA I) and ASPIRE (Study RA II). Concurrent use of stable doses of folic acid, oral corticosteroids (≤10 mg/day) and/or non-steroidal anti-inflammatory drugs (NSAIDs) was permitted.

Study RA I was a placebo-controlled study of 428 patients with active rheumatoid arthritis despite treatment with MTX. Patients enrolled had a median age of 54 years, median disease duration of 8.4 years, median swollen and tender joint count of 20 and 31 respectively and were on a median dose of 15 mg/wk of MTX. Patients received either placebo + MTX or one of 4 doses/schedules of Infliximab + MTX: 3 mg/kg or 10 mg/kg of Infliximab by intravenous (IV) infusion at Weeks 0, 2 and 6 followed by additional infusions every 4 or 8 weeks in combination with MTX.

Study RA II was a placebo-controlled study of 3 active treatment arms in 1004 MTX naive patients of 3 or fewer years' duration active rheumatoid arthritis. Patients enrolled had a median age of 51 years with a median disease duration of 0.6 years, median swollen and tender joint count of 19 and 31, respectively, and >80% of patients had baseline joint erosions. At randomization, all patients received MTX (optimized to 20 mg/wk by Week 8) and either placebo, 3 mg/kg or 6 mg/kg Infliximab at Weeks 0, 2, and 6 and every 8 weeks thereafter.

Data on use of Infliximab without concurrent MTX are limited.

Clinical Response

In Study RA I, all doses/schedules of Infliximab + MTX resulted in improvement in signs and symptoms as measured by the American College of Rheumatology response criteria (ACR 20) with a higher percentage of patients achieving an ACR 20, 50 and 70 compared to placebo + MTX (Table 6). This improvement was observed at Week 2 and maintained through Week 102. Greater effects on each component of the ACR 20 were observed in all patients treated with Infliximab + MTX compared to placebo + MTX (Table 6). More patients treated with Infliximab reached a major clinical response than placebo-treated patients (Table 6).

In Study RA II, after 54 weeks of treatment, both doses of Infliximab + MTX resulted in statistically significantly greater response in signs and symptoms compared to MTX alone as measured by the proportion of patients achieving ACR 20, 50 and 70 responses (Table 6). More

patients treated with Infliximab reached a major clinical response than placebo-treated patients (Table 6).

Table 6. ACR Response (percent of patients) in Adult RA Patients

	Study RA I					**Study RA II**		
		Infliximab + MTX				**Infliximab + MTX**		
		3 mg/kg		**10 mg/kg**			**3 mg/kg**	**6 mg/kg**
Response	**Placebo + MTX**	**q8 wks**	**q4 wks**	**q8 wks**	**q4 wks**	**Placebo + MTX**	**q8 wks**	**q8 wks**
	(n=88)	(n=86)	(n=86)	(n=87)	(n=81)	(n=274)	(n=351)	(n=355)
ACR 20								
Week 30	20%	50%[a]	50%[a]	52%[a]	58%[a]	N/A	N/A	N/A
Week 54	17%	42%[a]	48%[a]	59%[a]	59%[a]	54%	62%[c]	66%[a]
ACR 50								
Week 30	5%	27%[a]	29%[a]	31%[a]	26%[a]	N/A	N/A	N/A
Week 54	9%	21%[c]	34%[a]	40%[a]	38%[a]	32%	46%[a]	50%[a]
ACR 70								
Week 30	0%	8%[b]	11%[b]	18%[a]	11%[a]	N/A	N/A	N/A
Week 54	2%	11%[c]	18%[a]	26%	19%[a]	21%	33%[b]	37%[a]
Major Clinical Response*	0%	7%[c]	8%[b]	15%[a]	6%[c]	8%	12%	17%[a]

* A major clinical response was defined as a 70% ACR response for 6 consecutive months (consecutive visits spanning at least 26 weeks) through Week 102 for Study RA I and Week 54 for RA II.

[a] p≤0.001.

[b] p<0.01.

[c] P<0.05.

Table 7. Components of ACR 20 at Baseline and 54 Weeks (Study RA I)

	Placebo + MTX		**Infliximab + MTX[a]**	
Parameter (medians)	**(n=88)**		**(n=340)**	
	Baseline	**Week 54**	**Baseline**	**Week 54**
No. of Tender Joints	24	16	32	8
No. of Swollen Joints	19	13	20	7
Pain[b]	6.7	6.1	6.8	3.3
Physician's Global Assessment[b]	6.5	5.2	6.2	2.1
Patient's Global Assessment[b]	6.2	6.2	6.3	3.2
Disability Index (HAQ-DI)[c]	1.8	1.5	1.8	1.3
CRP (mg/dL)	3.0	2.3	2.4	0.6

[a] All doses/schedules of Infliximab + MTX.

[b] Visual Analog Scale (0=best, 10=worst).

[c] Health Assessment Questionnaire, measurement of 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities (0=best, 3=worst).

Radiographic Response
Structural damage in both hands and feet was assessed radiographically at Week 54 by the change from baseline in the van der Heijde-modified Sharp (vdH-S) score, a composite score of structural damage that measures the number and size of joint erosions and the degree of joint space narrowing in hands/wrists and feet.

In Study RA I, approximately 80% of patients had paired X-ray data at 54 weeks and approximately 70% at 102 weeks. The inhibition of progression of structural damage was observed at 54 weeks and maintained through 102 weeks. In Study RA II, >90% of patients had at least 2 evaluable X-rays. Inhibition of progression of structural damage was observed at Weeks 30 and 54 in the Infliximab + MTX groups compared to MTX alone. Patients treated with Infliximab + MTX demonstrated less progression of structural damage compared to MTX alone, whether baseline acute-phase reactants (ESR and CRP) were normal or elevated: patients with elevated baseline acute-phase reactants treated with MTX alone demonstrated a mean progression in vdH-S score of 4.2 units compared to patients treated with Infliximab + MTX who demonstrated 0.5 units of progression; patients with normal baseline acute phase reactants treated with MTX alone demonstrated a mean progression in vdH-S score of 1.8 units compared to Infliximab + MTX who demonstrated 0.2 units of progression. Of patients receiving Infliximab + MTX, 59% had no progression (vdH-S score $\leq$0 unit) of structural damage compared to 45% of patients receiving MTX alone. In a subset of patients who began the study without erosions, Infliximab + MTX maintained an erosion-free state at 1 year in a greater proportion of patients than MTX alone, 79% (77/98) vs. 58% (23/40), respectively (P<0.01). Fewer patients in the Infliximab + MTX groups (47%) developed erosions in uninvolved joints compared to MTX alone (59%).

Physical Function Response
Physical function and disability were assessed using the Health Assessment Questionnaire (HAQ-DI) and the general health-related quality of life questionnaire SF-36.

In Study RA I, all doses/schedules of Infliximab + MTX showed significantly greater improvement from baseline in HAQ-DI and SF-36 physical component summary score averaged over time through Week 54 compared to placebo + MTX, and no worsening in the SF-36 mental component summary score. The median (interquartile range) improvement from baseline to Week 54 in HAQ-DI was 0.1 (-0.1, 0.5) for the placebo + MTX group and 0.4 (0.1, 0.9) for Infliximab + MTX (p<0.001). Both HAQ-DI and SF-36 effects were maintained through Week 102. Approximately 80% of patients in all doses/schedules of Infliximab + MTX remained in the trial through 102 weeks.

In Study RA II, both Infliximab treatment groups showed greater improvement in HAQ-DI from baseline averaged over time through Week 54 compared to MTX alone; 0.7 for Infliximab +

MTX vs. 0.6 for MTX alone ($P \leq 0.001$). No worsening in the SF-36 mental component summary score was observed.

Ankylosing Spondylitis

The safety and efficacy of Infliximab were assessed in a randomized, multicenter, double-blind, placebo-controlled study in 279 patients with active ankylosing spondylitis. Patients were between 18 and 74 years of age and had ankylosing spondylitis as defined by the modified New York criteria for ankylosing spondylitis. Patients were to have had active disease as evidenced by both a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score >4 (possible range 0-10) and spinal pain >4 (on a visual analog scale [VAS] of 0-10). Patients with complete ankylosis of the spine were excluded from study participation, and the use of disease modifying anti-rheumatic drugs (DMARDs) and systemic corticosteroids were prohibited. Doses of Infliximab 5 mg/kg or placebo were administered intravenously at Weeks 0, 2, 6, 12 and 18.

At 24 weeks, improvement in the signs and symptoms of ankylosing spondylitis, as measured by the proportion of patients achieving a 20% improvement in ASAS response criteria (ASAS 20), was seen in 60% of patients in the Infliximab-treated group vs. 18% of patients in the placebo group (p<0.001). Improvement was observed at Week 2 and maintained through Week 24 (Table 8).

At 24 weeks, the proportions of patients achieving a 50% and a 70% improvement in the signs and symptoms of ankylosing spondylitis, as measured by ASAS response criteria (ASAS 50 and ASAS 70, respectively), were 44% and 28%, respectively, for patients receiving Infliximab, compared to 9% and 4%, respectively, for patients receiving placebo (P<0.001, Infliximab vs. placebo). A low level of disease activity (defined as a value <20 [on a scale of 0-100 mm] in each of the 4 ASAS response parameters) was achieved in 22% of Infliximab-treated patients vs. 1% in placebo-treated patients (P<0.001).

Table 8. Components of Ankylosing Spondylitis Disease Activity

	Placebo (n=78)		**Infliximab 5mg/kg (n=201)**		
	Baseline	**24 Weeks**	**Baseline**	**24 Weeks**	**P-value**
ASAS 20 response					
Criteria (Mean)					
Patient Global Assessment[a]	6.6	6.0	6.8	3.8	<0.001
Spinal pain[a]	7.3	6.5	7.6	4.0	<0.001
BASFI[b]	5.8	5.6	5.7	3.6	<0.001
Inflammation[c]	6.9	5.8	6.9	3.4	<0.001
Acute Phase Reactants					
Median CRP[d] (mg/dL)	1.7	1.5	1.5	0.4	<0.001
Spinal Mobility (cm, Mean)					
Modified Schober's test[e]	4.0	5.0	4.3	4.4	0.75

Chest expansion[e]	3.6	3.7	3.3	3.9	0.04
Tragus to wall[e]	17.3	17.4	16.9	15.7	0.02
Lateral spinal flexion[e]	10.6	11.0	11.4	12.9	0.03

[a] Measured on a VAS with 0= "none" and 10= "severe".
[b] Bath Ankylosing Spondylitis Functional Index (BASFI), average of 10 questions.
[c] Inflammation, average of last 2 questions on the 6-question BASDAI.
[d] CRP normal range 0-1.0 mg/dL.
[e] Spinal mobility normal values; modified Schober's test: >4 cm; chest expansion: >6 cm; tragus to wall: <15 cm; lateral spinal flexion: >10 cm.

The median improvement from baseline in the general health-related quality-of-life questionnaire SF-36 physical component summary score at Week 24 was 10.2 for the Infliximab group vs. 0.8 for the placebo group (*P*<0.001). There was no change in the SF-36 mental component summary score in either the Infliximab group or the placebo group.

Results of this study were similar to those seen in a multicenter double-blind, placebo-controlled study of 70 patients with ankylosing spondylitis.

Psoriatic Arthritis

Safety and efficacy of Infliximab were assessed in a multicenter, double-blind, placebo-controlled study in 200 adult patients with active psoriatic arthritis despite DMARD or NSAID therapy (≥5 swollen joints and ≥5 tender joints) with 1 or more of the following subtypes: arthritis involving distal interphalangeal (DIP) joints (n=49), arthritis mutilans (n=3), asymmetric peripheral arthritis (n=40), polyarticular arthritis (n=100), and spondylitis with peripheral arthritis (n=8). Patients also had plaque psoriasis with a qualifying target lesion ≥2 cm in diameter. Forty-six percent of patients continued stable doses of MTX (≤25 mg/week). During the 24-week double-blind phase, patients received either 5 mg/kg Infliximab or placebo at Weeks 0, 2, 6, 14, and 22 (100 patients in each group). At Week 16, placebo patients with <10% improvement from baseline in both swollen and tender joint counts were switched to Infliximab induction (early escape). At Week 24, all placebo-treated patients crossed over to Infliximab induction. Dosing continued for all patients through Week 46.

Clinical Response

Treatment with Infliximab resulted in improvement in signs and symptoms, as assessed by the ACR criteria, with 58% of Infliximab-treated patients achieving ACR 20 at Week 14, compared with 11% of placebo-treated patients (*P*<0.001). The response was similar regardless of concomitant use of MTX. Improvement was observed as early as Week 2. At 6 months, the ACR 20/50/70 responses were achieved by 54%, 41%, and 27%, respectively, of patients receiving Infliximab compared to 16%, 4%, and 2%, respectively, of patients receiving placebo. Similar responses were seen in patients with each of the subtypes of psoriatic arthritis, although few patients were enrolled with the arthritis mutilans and spondylitis with peripheral arthritis subtypes.

Compared to placebo, treatment with Infliximab resulted in improvements in the components of the ACR response criteria, as well as in dactylitis and enthesopathy (Table 9). The clinical response was maintained through Week 54. Similar ACR responses were observed in an earlier randomized, placebo-controlled study of 104 psoriatic arthritis patients, and the responses were maintained through 98 weeks in an open-label extension phase.

Table 9. Components of ACR 20 and Percentage of Patients with 1 or More Joints with Dactylitis and Percentage of Patients with Enthesopathy at Baseline and Week 24

	Placebo		**Infliximab 5 mg/kg[a]**	
Patients Randomized	**(n=100)**		**(n=100)**	
	Baseline	**Week 24**	**Baseline**	**Week 24**
Parameter (medians)				
No. of Tender Joints[b]	24	20	20	6
No. of Swollen Joints[c]	12	9	12	3
Pain[d]	6.4	5.6	5.9	2.6
Physician's Global Assessment[d]	6.0	4.5	5.6	1.5
Patient's Global Assessment[d]	6.1	5.0	5.9	2.5
Disability Index (HAQ-DI)[e]	1.1	1.1	1.1	0.5
CRP (mg/dL)[f]	1.2	0.9	1.0	0.4
% Patients with 1 or more digits with dactylitis	41	33	40	15
% Patients with enthesopathy	35	36	42	22

[a] P<0.001 for percent change from baseline in all components of ACR 20 at Week 24, P<0.05 for % of patients with dactylitis, and P=0.004 for % of patients with enthesopathy at Week 24.
[b] Scale 0-68.
[c] Scale 0-66.
[d] Visual Analog Scale (0=best, 10=worst).
[e] Health Assessment Questionnaire, measurement of 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities (0=best, 3=worst).
[f] Normal range 0-0.6 mg/dL.

Improvement in Psoriasis Area and Severity Index (PASI) in psoriatic arthritis patients with baseline body surface area (BSA) ≥3% (n=87 placebo, n=83 Infliximab) was achieved at Week 14, regardless of concomitant MTX use, with 64% of Infliximab-treated patients achieving at least 75% improvement from baseline vs. 2% of placebo-treated patients; improvement was observed in some patients as early as Week 2. At 6 months, the PASI 75 and PASI 90 responses were achieved by 60% and 39%, respectively, of patients receiving Infliximab compared to 1% and 0%, respectively, of patients receiving placebo. The PASI response was generally maintained through Week 54.

Radiographic Response
Structural damage in both hands and feet was assessed radiographically by the change from baseline in the van der Heijde-Sharp (vdH-S) score, modified by the addition of hand DIP joints. The total modified vdH-S score is a composite score of structural damage that measures the

number and size of joint erosions and the degree of joint space narrowing (JSN) in the hands and feet. At Week 24, Infliximab-treated patients had less radiographic progression than placebo-treated patients (mean change of -0.70 vs. 0.82, *P*<0.001). Infliximab-treated patients also had less progression in their erosion scores (-0.56 vs. 0.51) and JSN scores (-0.14 vs. 0.31). The patients in the Infliximab group demonstrated continued inhibition of structural damage at Week 54. Most patients showed little or no change in the vdH-S score during this 12-month study (median change of 0 in both patients who initially received Infliximab or placebo). More patients in the placebo group (12%) had readily apparent radiographic progression compared with the Infliximab group (3%).

Physical Function
Physical function status was assessed using the HAQ Disability Index (HAQDI) and the SF-36 Health Survey. Infliximab-treated patients demonstrated significant improvement in physical function as assessed by HAQ-DI (median percent improvement in HAQ-DI score from baseline to Week 14 and 24 of 43% for Infliximab-treated patients vs. 0% for placebo-treated patients). During the placebo-controlled portion of the trial (24 weeks), 54% of Infliximab-treated patients achieved a clinically meaningful improvement in HAQ-DI (≥0.3-unit decrease) compared to 22% of placebo-treated patients. Infliximab-treated patients also demonstrated greater improvement in the SF-36 physical and mental component summary scores than placebo-treated patients. The responses were maintained for up to 2 years in an open-label extension study.

<u>Plaque Psoriasis</u>
The safety and efficacy of Infliximab were assessed in 3 randomized, double-blind, placebo-controlled studies in patients 18 years of age and older with chronic, stable plaque psoriasis involving ≥10% BSA, a minimum PASI score of 12, and who were candidates for systemic therapy or phototherapy. Patients with guttate, pustular, or erythrodermic psoriasis were excluded from these studies. No concomitant anti-psoriatic therapies were allowed during the study, with the exception of low-potency topical corticosteroids on the face and groin after Week 10 of study initiation.

Study I (EXPRESS) evaluated 378 patients who received placebo or Infliximab at a dose of 5 mg/kg at Weeks 0, 2, and 6 (induction therapy), followed by maintenance therapy every 8 weeks. At Week 24, the placebo group crossed over to Infliximab induction therapy (5 mg/kg), followed by maintenance therapy every 8 weeks. Patients originally randomized to Infliximab continued to receive Infliximab 5 mg/kg every 8 weeks through Week 46. Across all treatment groups, the median baseline PASI score was 21 and the baseline Static Physician Global Assessment (sPGA) score ranged from moderate (52% of patients) to marked (36%) to severe (2%). In addition, 75% of patients had a BSA >20%. Seventy-one percent of patients previously received systemic therapy, and 82% received phototherapy.

Study II (EXPRESS II) evaluated 835 patients who received placebo or Infliximab at doses of 3 mg/kg or 5 mg/kg at Weeks 0, 2, and 6 (induction therapy). At Week 14, within each Infliximab dose group, patients were randomized to either scheduled (every 8 weeks) or as needed (PRN)

maintenance treatment through Week 46. At Week 16, the placebo group crossed over to Infliximab induction therapy (5 mg/kg), followed by maintenance therapy every 8 weeks. Across all treatment groups, the median baseline PASI score was 18, and 63% of patients had a BSA >20%. Fifty-five percent of patients previously received systemic therapy, and 64% received a phototherapy.

Study III (SPIRIT) evaluated 249 patients who had previously received either psoralen plus ultraviolet A treatment (PUVA) or other systemic therapy for their psoriasis. These patients were randomized to receive either placebo or Infliximab at doses of 3 mg/kg or 5 mg/kg at Weeks 0, 2, and 6. At Week 26, patients with a sPGA score of moderate or worse (greater than or equal to 3 on a scale of 0 to 5) received an additional dose of the randomized treatment. Across all treatment groups, the median baseline PASI score was 19, and the baseline sPGA score ranged from moderate (62% of patients) to marked (22%) to severe (3%). In addition, 75% of patients had a BSA >20%. Of the enrolled patients, 114 (46%) received the Week 26 additional dose.

In Studies I, II and III, the primary endpoint was the proportion of patients who achieved a reduction in score of at least 75% from baseline at Week 10 by the PASI (PASI 75). In Study I and Study III, another evaluated outcome included the proportion of patients who achieved a score of "cleared" or "minimal" by the sPGA. The sPGA is a 6-category scale ranging from "5 = severe" to "0 = cleared" indicating the physician's overall assessment of the psoriasis severity focusing on induration, erythema, and scaling. Treatment success, defined as "cleared" or "minimal," consisted of none or minimal elevation in plaque, up to faint red coloration in erythema, and none or minimal fine scale over <5% of the plaque.

Study II also evaluated the proportion of patients who achieved a score of "clear" or "excellent" by the relative Physician's Global Assessment (rPGA). The rPGA is a 6-category scale ranging from "6 = worse" to "1 = clear" that was assessed relative to baseline. Overall lesions were graded with consideration to the percent of body involvement as well as overall induration, scaling, and erythema. Treatment success, defined as "clear" or "excellent," consisted of some residual pinkness or pigmentation to marked improvement (nearly normal skin texture; some erythema may be present). The results of these studies are presented in Table 10.

Table 10. Psoriasis studies I, II, and III, Week 10 Percentage of Patients Who Achieved PASI 75 and Percentage Who Achieved Treatment "Success" with Physician's Global Assessment

	Placebo	**Infliximab**	
		3 mg/kg	**5 mg/kg**
Psoriasis Study 1 – patients randomized[a]	77	-	301
PASI 75	2 (3%)	-	242 (80%)*
sPGA	3 (4%)	-	242 (80%)*
Psoriasis Study II – patients randomized[a]	208	313	314
PASI 75	4 (2%)	220 (70%)*	237 (75%)*
rPGA	2 (1%)	217 (69%)*	234 (75%)*

Psoriasis Study III – patients randomized[b]	51	99	99
PASI 75	3 (6%)	71 (72%)*	87 (88%)*
sPGA	5 (10%)	71 (72%)*	89 (90%)*

* P<0.001 compared with placebo.

[a] Patients with missing data at Week 10 were considered as nonresponders.

[b] Patients with missing data at Week 10 were imputed by last observation.

In Study I, in the subgroup of patients with more extensive psoriasis who had previously received phototherapy, 85% of patients on 5 mg/kg Infliximab achieved a PASI 75 at Week 10 compared with 4% of patients on placebo. In Study II, in the subgroup of patients with more extensive psoriasis who had previously received phototherapy, 72% and 77% of patients on 3 mg/kg and 5 mg/kg Infliximab achieved a PASI 75 at Week 10 respectively compared with 1% on placebo. In Study II, among patients with more extensive psoriasis who had failed or were intolerant to phototherapy, 70% and 78% of patients on 3 mg/kg and 5 mg/kg Infliximab achieved a PASI 75 at Week 10 respectively, compared with 2% on placebo.

Maintenance of response was studied in a subset of 292 and 297 Infliximab-treated patients in the 3 mg/kg and 5 mg/kg groups; respectively, in Study II. Stratified by PASI response at Week 10 and investigational site, patients in the active treatment groups were re-randomized to either a scheduled or as needed maintenance (PRN) therapy, beginning on Week 14.

The groups that received a maintenance dose every 8 weeks appeared to have a greater percentage of patients maintaining a PASI 75 through Week 50 as compared to patients who received the as-needed or PRN doses, and the best response was maintained with the 5 mg/kg every 8-week dose. These results are shown in Figure 4. At Week 46, when Infliximab serum concentrations were at trough level, in the every 8-week dose group, 54% of patients in the 5 mg/kg group compared to 36% in the 3 mg/kg group achieved PASI 75. The lower percentage of PASI 75 responders in the 3 mg/kg every 8-week dose group compared to the 5 mg/kg group was associated with a lower percentage of patients with detectable trough serum infliximab levels. This may be related in part to higher antibody rates. In addition, in a subset of patients who had achieved a response at Week 10, maintenance of response appears to be greater in patients who received Infliximab every 8 weeks at the 5 mg/kg dose. Regardless of whether the maintenance doses are PRN or every 8 weeks, there is a decline in response in a subpopulation of patients in each group over time. The results of Study I through Week 50 in the 5 mg/kg every 8 weeks maintenance dose group were similar to the results from Study II.

Efficacy and safety of Infliximab treatment beyond 50 weeks have not been evaluated in patients with plaque psoriasis.

Off-Label Indications

Granulomatosis with Polyangiitis

Multiple case series have been performed to study the effect of infliximab in the treatment of refractory Wegener's granulomatosis. Findings consistently found infliximab treatment led to

symptomatic improvement and may provide an effective and more specific therapeutic option in the treatment of active Wegener's granulomatosis refractory to standard treatment. (7-9)

Hidradenitis Suppurativa

Gulliver et al. (2016) published an evidence-based approach to the treatment of hidradenitis suppurativa/acne inversa based on the European guidelines for hidradenitis suppurativa. (10) While adalimumab is considered for first line biologic therapy, if there is no response after 16 weeks of adalimumab treatment, other treatments should be considered. Infliximab is considered as a second line biologic treatment option.

Juvenile idiopathic arthritis

Systematic Reviews

Most of the published literature on the use of infliximab for the treatment of JIA has not distinguished between the disease subtypes. Kemper et al. (2011) conducted a comparative effectiveness review for the Agency for Healthcare Quality on the use of disease modifying antirheumatic drugs (DMARDs) for children with JIA. (11) Reviewers found that evidence on biologic DMARDs was limited, although symptom improvement was reported. Heterogeneity of studies and outcome reporting, as well as varied categories of JIA, made meaningful comparisons of DMARDs difficult.

An evidence based review by Shenoi and Wallace (2010) noted that infliximab is frequently used to treat JIA in clinical practice, despite not having the Food and Drug Administration (FDA) approval for this indication. (12)

Randomized Controlled Trials

Ruperto et al. (2010) reported on an open label extension trial of infliximab for JIA in 78 children. (13) However, this study was limited by the high number of patients who discontinued infliximab treatment (42 [58%] patients) for various reasons. Of the remaining 36 patients, 40% achieved American College of Rheumatology Pediatric 50 response criteria at week 204, whereas 33% achieved American College of Rheumatology Pediatric 70 during this time period. Thirteen percent of patients achieved inactive disease status.

In a report of a multicenter, 54-week, randomized, open label trial of JIA (n=60) by Tynjala et al. (2011), patients taking infliximab plus MTX had better outcomes than those taking MTX alone or in combination with sulfasalazine and hydroxychloroquine. (14) In patients taking infliximab, all 19 achieved American College of Rheumatology Pediatric 75 compared with 13 (65%) of 20 on combination treatment and 10 (50%) of 20 on MTX. Thirteen (68%) of patients taking infliximab achieved inactive disease status compared with 8 (40%) and 5 (25%) in the combination and MTX groups, respectively. The inactive disease also continued for a longer duration in the infliximab group (mean, 26 weeks) than in the combination and MTX groups (mean, 13 weeks and 6 weeks).

Case Series

The literature on the use of infliximab to treat systemic JIA is limited to case reports in children refractory to first line treatment or other biologic products. (15-16)

Sarcoidosis

Maneiro et al. (2012) conducted a systematic review of sarcoidosis treatment with TNF blockers. (17) Reviewers found insufficient evidence to support the use of TNF blockers for the treatment of sarcoidosis.

Analyses from a previously published randomized trial of 138 patients with pulmonary sarcoidosis were reported by Judson et al. (2008). (18) Patients received infliximab or placebo for 24 weeks. An outcome metric designed for the study, the Physician Organ Severity Tool, summarized the involvement of 17 extrapulmonary organs. Although a statistical improvement in group mean score was noted at 24 weeks with infliximab, the outcome metric had not been clinically validated, and its relation to clinical outcomes was unknown. In a 2011 publication from the same authors, levels of inflammatory serum proteins were reduced in 134 sarcoidosis patients who received infliximab in the original trial. (19)

Still's Disease

Kraetsch and colleagues (2001) examined the efficacy of infliximab in the treatment of patients with severe and active adult-onset Still's disease (AOSD) despite conventional immunosuppressive therapy. (20) A total of 6 patients with the diagnosis of AOSD according to the Yamagushi criteria of 1992 were treated with infliximab. All patients had severe disease with high clinical and serological activity. Patients were treated initially with high dose steroids or more intensive immunosuppressive therapy. Two patients had a history of multiple disease modifying antirheumatic drug (DMARD) treatments. One patient had a history of 3 years of AOSD with fever, chills, pleural and pericardial effusions, and hepatosplenomegaly. Despite these treatments, the patient developed increasing serological signs of inflammation and arthritis of both hips and peripheral joints. Another patient had a history of 5 years of AOSD with oligoarthritis, myalgias, and recurrent fever despite multiple DMARD treatment, including cyclophosphamide pulse therapy. These patients with AOSD presented with massive polyarthralgias, polyarthritis, splenomegaly or hepatomegaly, the typical rash, sore throat, weight loss, serositis, continuing fever, leucocytosis, and raised C reactive protein (CRP), ESR, and ferritin levels. Four patients with early onset of the disease, fulfilling the diagnostic criteria for AOSD and a clinical and serological high disease activity, were included in this pilot study without any further DMARD treatment apart from the initial steroid treatment. Reduction of established treatment, mainly with steroids, caused a relapse of the disease in all these patients. Patients then received 3 to 5 mg/kg infliximab on weeks 0, 2, and 6, continuing with intervals of 6 to 8 weeks depending on the patient's individual disease activity. In all patients, fever, arthralgias, myalgias, hepatosplenomegaly, and the rash resolved after the first courses of treatment with infliximab. All serological variables (CRP, ESR, hyperferritinaemia) returned to normal. After 3 courses of infliximab infusions, splenomegaly could not be detected in any of these patients. After 3 courses of treatment with infliximab, splenomegaly could not be detected in any of the patients. Up to now, these patients have received infliximab infusion treatment for between 5 and 28 months. Throughout this period, all patients have continued to

benefit from this treatment, with improvement in their clinical symptoms, joint counts, and serological disease activity. One of the patients had a moderate infusion reaction during the second treatment. The infusion was discontinued for 1 hour and then was resumed with no further problems. The authors concluded that the disease improved remarkably in all 6 patients with AOSD after treatment with infliximab, also in the early stage of AOSD. These preliminary data suggested the potential therapeutic benefit of anti-TNF-alpha treatment in AOSD.

In a prospective, non-comparative case-series study, Kokkinos et al. (2004) examined the effects of infliximab on refractory AOSD. (21) A total of 4 patients with severe and highly active AOSD, refractory to high doses of corticosteroids (which had been combined with MTX in 3 of them) and MTX were treated with infliximab (initial dose 3 to 5 mg/kg, continuing at intervals depending on the patient's individual disease activity). Resolution of their symptoms, which was evident within few days after the first infusion, and a parallel rapid improvement of the acute inflammatory response indices were observed in all. Concomitant corticosteroid treatment was reduced after the first courses of treatment with infliximab, which was well-tolerated, and complete disease remission was sustained during a 5 to18 months follow-up period. The authors noted that although further studies are needed to confirm long-term efficacy and safety in larger numbers of patients, they suggested that administration of infliximab with observation for objective improvement is the treatment of choice in cases of AOSD refractory to conventional treatment.

Synovitis

In a randomized, placebo-controlled study of infliximab therapy in early RA, Taylor et al. (2004) patients were randomly assigned to receive blinded infusions of 5 mg/kg infliximab (n = 12) or placebo (n = 12) at weeks 0, 2, 6, and then every 8 weeks until week 46. At baseline and week 18, clinical assessments were performed, and metacarpophalangeal joints were assessed by high-frequency ultrasonography and power Doppler ultrasonography measurements. Radiographs of the hands and feet taken at baseline and at 54 weeks were evaluated using the van der Heijde modification of the Sharp method (vdH-Sharp score). Using changes in the total vdH-Sharp score over 54 weeks and changes in synovial thickening and joint vascularity at 18 weeks, investigators were able to distinguish those patients receiving infusions of infliximab + MTX from those receiving placebo + MTX. Sonographic measurements of synovial thickening and vascularity at baseline in the placebo + MTX group demonstrated clear relationships with the magnitude of radiologic joint damage at week 54. Infliximab + MTX treatment abolished these relationships. (22)

In 2005, Quinn et al. conducted a 12-month double-blind study that looked at remission induction using standard therapy with or without infliximab in patients with early, poor-prognosis RA. (23) The primary end point was synovitis. Clinical observation continued to 24 months. Twenty patients were recruited (mean age 52 years, mean symptom duration 6 months, mean C-reactive protein level 42 mg/liter, and 65% rheumatoid factor positive). At 1 year, all MRI scores were significantly better, with no new erosions in the infliximab plus MTX group; a greater percentage of infliximab plus MTX-treated patients fulfilled the American College of Rheumatology 50% and 70% improvement criteria (78% versus 40% in the placebo

plus MTX group and 67% versus 30%, respectively) and had a greater functional benefit (P < 0.05 for all comparisons). Importantly, at 1 year after stopping induction therapy, response was sustained in 70% of the patients in the infliximab plus MTX group, with a median Disease Activity Score in 28 joints (DAS28) of 2.05 (remission range). At 2 years, there were no significant between-group differences in the DAS28, ACR response, or radiographic scores, but differences in the Health Assessment Questionnaire and RA Quality of Life scores were maintained (P < 0.05). Remission induction with infliximab plus MTX provided a significant reduction in MRI evidence of synovitis and erosions at 1 year. At 2 years, functional and quality of life benefits were sustained, despite withdrawal of infliximab therapy.

Takayasu's Disease

Filocamo et al. (2008) noted that 4 children with Takayasu's disease were treated with TNF antagonists because of disease relapse during conventional therapy or as a first-line agent. (24) Two patients went into remission; in the other 2, the response was partial. The authors concluded that anti-TNF agents can have a role in the treatment of Takayasu's disease; however, further controlled studies are needed.

In a retrospective study, Molloy et al. (2008) assessed the efficacy of anti-TNF therapy to induce remission in patients with Takayasu's disease refractory to other immunosuppressive therapies. (25) Patients (n = 25) were treated with infliximab (IFX) or etanercept (ETA) for up to 7 years; 21 with IFX (median 28 months; range of 2 to 84) and 9 with ETA (median 28 months; range of 4 to 82); 5 patients initially treated with ETA subsequently switched to IFX. Following anti-TNF therapy, remission was achieved, and prednisone was discontinued in 15 patients (60 %) and successfully tapered below 10 mg/day in an additional 7 patients (28 %). Of 18 patients treated with other immunosuppressive agents concurrent with anti-TNF therapy, 9 (50 %) could taper or discontinue the additional agent. Major relapses occurred in 4 patients that initially achieved stable remission. Four patients suffered adverse events, including 1 with opportunistic infections and 1 with breast cancer. The authors concluded that in this group of patients with refractory Takayasu's disease, anti-TNF therapy was associated with remission in a majority of patients, facilitating dose reduction or discontinuation of prednisone and other immunosuppressive therapy.

Uveitis

Tynjälä et al. (2007) evaluated the efficacy of anti-tumour necrosis factor (anti-TNF) treatment in juvenile idiopathic arthritis (JIA) associated uveitis. (26) Twenty-four patients with uveitis taking etanercept and 21 taking infliximab were studied. The endpoint ophthalmological evaluation was at 24 months or at the termination of the first biological agent. The ocular inflammatory activity was graded on the basis of the number of anterior chamber cells. Of the 45 patients, uveitis improved in 14 (31%), no change was observed in 14 (31%) and the activity of uveitis increased in 17 (38%). Inflammatory activity improved more frequently (p = 0.047) in the patients taking infliximab than in those taking etanercept. The number of uveitis flares/year was higher (p = 0.015) in the patients taking etanercept (mean 1.4, range 0–3.2) than in those taking infliximab (mean 0.7, range 0–2). Uveitis developed for the first time while taking anti-TNF treatment in five patients-taking etanercept (2.2/100 patient years) and 1 taking infliximab

(1.1/100 patient-years). Researchers concluded that during anti-TNF treatment, the ophthalmological condition improved in one-third of the patients with uveitis. In chronic anterior uveitis, associated with refractory JIA, infliximab may be more effective than etanercept.

In a retrospective case series, Ardoin et al. (2007) reviewed the course of 16 children with noninfectious uveitis treated with infliximab at an academic medical center. (27) Outcome measures included incidence of uveitis recurrences, proportion of patients achieving zero or two-step decline in ocular inflammation, visual acuity, and proportion discontinuing topical glucocorticoids at zero, three, six, nine, and 12 months of therapy. Of sixteen children (29 affected eyes) with median age 11 years, six had associated extraocular inflammatory conditions. Fifteen of 16 were treated with concomitant MTX. Median follow-up was 26 months and median maintenance infliximab dose was 8.2 mg/kg. The median interval between infliximab infusions was 5.6 weeks. At one year, 64% achieved zero ocular inflammation, and 79% had zero inflammation or a two-step decline in inflammation. Topical glucocorticoids were discontinued in 69%, and 58% remained free of uveitis recurrence at one year. Visual acuity remained stable. Infliximab was discontinued in two children, one because of inefficacy and the other because of parental concern about potential side effects. No adverse events occurred.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J1745, J3590, Q5103, Q5104, Q5109, Q5121

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change

02/01/2025	Document updated. The following change was made to Coverage: Added language regarding drug shortages/recalls to "Initial Therapy" criteria. No new references added.
06/01/2024	Document updated. The following change was made to Continuation Therapy in Coverage: removed "through a previously authorized pharmacy or medical benefit" in the statement "Continuation of Renflexis or Ixifi may be considered medically necessary for all members (including new members…" Now reads: "Continuation of Renflexis or Ixifi may be considered medically necessary for all Members (including new members): who are currently receiving the requested medication for an indication listed below, AND who are experiencing benefit from therapy as evidenced by disease stability or disease improvement, AND when dosing is in accordance with an authoritative source." No new references added.
09/15/2023	Document updated with literature review. Coverage unchanged. No new references added; some updated and one removed.
03/01/2023	Document updated with literature review. The following changes were made to Coverage: 1) FDA-labeled indications table revised to remove the products column. 2) Revised the off-label indication statement from Infliximab (Remicade® and Infliximab (unbranded) to Infliximab and infliximab biosimilars; 3) removed Colitis (severe), immune-related, associated with anti-PD1 agents and ipilimumab that does not respond within 1 week to therapy with high-dose steroids (single dose) from the list of off-label indications; 4) revised NOTE 1 to read: This medical policy does NOT address oncologic indications. This medical policy IS NOT TO BE USED for oncologic indications. Refer to RX502.061 Oncology Medications for oncologic indications. 5) Added NOTE 2: Infliximab and infliximab biosimilars shall not be used concurrently with other biologics used to treat the indications above. Please refer to the Description Section for a list of biological disease-modifying antirheumatic drugs (DMARDs). Added table to Description with list of disease-modifying antirheumatic drugs (DMARDs). References revised; some removed; none added.
04/01/2022	Document updated with: 1) modified preferred drug language/criteria, and 2) addition of Infliximab (unbranded) to the list of infliximab products.
12/01/2021	Document updated with literature review. No change in coverage. References updated, none added.
10/01/2020	Document update with literature review. The following changes were made to Coverage: 1) Added Ixifi and Avsola to the non-preferred product section; 2) Added Avsola® (infliximab-axxq) to the list of infliximab products; 3) Separated label and off-label medically necessary indications for infliximab products; 4) Clarified that label language for ankylosing spondylitis and rheumatoid arthritis is specific to adults; 5) Added "NOTE 1: Currently there is no medically accepted off-label use of any of the infliximab biosimilars."; 5) Removed all other drug products from policy so that it is now specific to

	infliximab and associated biosimilars – certolizumab pergol, golimumab, abatacept, ustekinumab, tocilizumab, belimumab, vedolizumab, canakinumab, and pegloticase are now addressed in individual policies. All references added and/or updated. Title changed from "Biologic Response Modifiers (BRMs) for the Treatment of Rheumatoid Arthritis (RA) and Other Chronic Inflammatory Diseases".
08/20/2020	Document updated with literature review. The following change was made to Coverage criteria for Stelara® (ustekinumab): Revised indications to address only those for intravenous (IV) administration.
07/15/2020	Document updated with literature review. The following changes were made to Coverage criteria for Tocilizumab (Actemra®): 1) Revised to indicate policy is specific to intravenous (IV) administration only; and 2) Removed giant cell arteritis.
04/01/2020	The following was added to the Coverage: Remicade ®(infliximab) and Inflectra™ (infliximab-dyyb) are the preferred infliximab products. Coverage will be provided for Remicade® and Inflectra™ (infliximab-dyyb) contingent on the coverage criteria in this Medical Policy. Coverage for Renflexis™ (infliximab-abda) will be provided contingent on the criteria in this section and the coverage criteria in the Medical Policy. Patients currently on Renflexis™ (infliximab-abda) will be allowed to continue therapy for the duration of their previous pre-determination period. Upon renewal of a pre-determination, patients on Renflexis™ (infliximab-abda) or patients initiating therapy with an infliximab product, the following criteria would apply prior to Renflexis use: Patient has tried and failed, or is intolerant to, or has a clinical contraindication to Remicade ®(infliximab) and Inflectra™ (infliximab-dyyb); AND Physician attests that in their clinical opinion, the same intolerance, contraindication, lack of clinical efficacy, or adverse event would not be expected to occur with Renflexis or other infliximab product. State specific drug criteria may apply. Coverage added for Stelara to include FDA approved indication for moderately to severely active ulcerative colitis.
07/15/2018	Document updated with literature review. The following added: 1) Specific to Remicade® (Infliximab) the following biosimilar wording added: Ixifi (infliximab-qbtx, Biosimilar). In addition, the following medically necessary indications added for Remicade: "Adult onset Still's disease; granulomatosis with polyangiitis, refractory, in combination with corticosteroids; hidradenitis suppurativa, severe, refractory; juvenile idiopathic arthritis (severe), refractory to other therapies; takayasu's disease, refractory; uveitis, refractory, adjunct; severe immune-related colitis associated with anti-PD1 agents and ipilimumab that does not respond within 1 week to therapy with high-dose steroids (single dose)." 2) Specific to Actemra for rheumatoid arthritis, the following wording was removed from the medically necessary coverage: "who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs)"; In addition, the following new indication added: "Indicated for adults and pediatric patients 2 years of age

	and older with chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome". 3) Specific to Kineret the following indication was added: "Chronic infantile neurological, cutaneous and articular syndrome, treatment-refractory". 4) Specific to Ilaris the following indication was added: "Gouty arthritis, acute". 5) Specific to Orencia the following indications were added: "Rheumatoid arthritis, early disease, methotrexate naive with poor prognostic factors; and "adult Psoriatic Arthritis (PsA)". 6) For Kystexxa the criteria for baseline uric acid level changed from "at least 8 mg/dL to "at least 6 mg/dL".
02/15/2018	Partial update. Coverage criteria wording for Stelara® (ustekinumab) specific to severe plaque psoriasis (Ps) changed from "adults" to now state "12 years or older". The other two indications for Stelara for adults had the following wording added: "18 years and older". In addition, specific to Simponi Aria® (golimumab), the following two indications were added: active psoriatic arthritis (PsA) and active ankylosing spondylitis (AS).
08/15/2017	Partial update. The coverage statement "Is considered experimental, investigational and unproven for all other indications" was added to the coverage sections for Stelara and Ilaris.
07/15/2017	Partial update. The following new FDA approved indication was added to coverage for Actemra: "Indicated for adult patients with giant cell arteritis.
04/01/2017	Document updated with literature review. The following was added to the coverage section: 1) Stelara® is indicated for the treatment of adult patients with: Moderate to severe plaque psoriasis (Ps) who are candidates for phototherapy or systemic therapy, active psoriatic arthritis (PsA), alone or in combination with methotrexate, or moderately to severely active Crohn's disease (CD) who have failed or were intolerant to: Treatment with immunomodulators or corticosteroids, but never failed a tumor necrosis factor (TNF) blocker, or failed or were intolerant to treatment with one or more TNF blockers. In addition, the following note was added specific to Stelara. "Note: When meeting criteria noted above adults with Crohn's disease will receive the first dose of Stelara through a vein in the arm (intravenous infusion) in a healthcare facility by a healthcare provider. Patients may then receive Stelara as an injection under the skin (subcutaneous injection) 8 weeks after the first dose." 2) The following indications were added to the coverage indications for Ilaris for adult and pediatric patients: Tumor Necrosis Factor (TNF) receptor Associated Periodic Syndrome (TRAPS), Hyperimmunoglobulin D (Hyper-IgD) Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD), and Familial Mediterranean Fever (FMF).
03/15/2016	Reviewed. No changes.
12/15/2015	Document updated with literature review. 1) The following was removed from the Remicade coverage specific to ankylosing spondylitis and psoriatic arthritis: "Patients with ankylosing spondylitis or psoriatic arthritis who are

	refractory to conventional therapies" and 2) The coverage statement for Remicade specific to ulcerative colitis modified to remove the word "achieving" and replaced with "inducing and maintaining". The coverage reads: "Reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy".
11/15/2015	Document updated with literature review. The following was changed: Specific coverage criteria for Humira, Enbrel, and Stelara was removed and replaced with the following statement: "This biologic response modifier (BRM) is self-administered. Please refer to applicable pharmacy benefit plan".
10/01/2014	Document updated with literature review. The coverage section has been updated to reflect the U. S. Food and Drug Administration (FDA) approved drug Entyvio. Conditional coverage statement is based on FDA labeled indications for ulcerative colitis and Crohn's disease (see coverage). CPT/HCPCS code(s) updated.
01/01/2014	Document updated with literature review. The coverage section has been updated to reflect revised or addition approved FDA indications for the following biologics: Cimzia, Simponi, Simponi Aria, and Stelara. CPT/HCPCS code(s) updated
08/15/2013	Document updated with literature review. This coverage section has been updated to reflect revised or additional approved FDA indications (since the time of the last medical policy update), for the following biologics: Remicade, Humira, Actemra, Kineret, and Ilaris (see coverage).
10/01/2011	Document updated with literature review. The following was added: Use of Amevive for specific FDA approved indications may be considered medically necessary when noted criteria are met.
07/01/2011	Document updated with literature review. The following was added: Use of Rituxan, Actemra, Krystexxa, and Benlysta for specific FDA approved indications may be considered medically necessary when noted criteria are met. All other indications are considered experimental, investigational, and unproven.
03/15/2010	Revised/updated entire document specific to the new FDA approved drug Actemra. Actemra is indicated for treatment of adult patients with moderately-to severely-active RA who have had an inadequate response to one or more TNF antagonist therapies. Actemra may be used as monotherapy or concomitantly with methotrexate or other DMARDs.
11/15/2009	Revised/updated entire document. Coverage position remains conditional with the addition of new RA indication for Cimzia and new coverage statement for drug Simponi and Stelara with coverage criteria based on FDA labeled indications.
10/01/2008	Revised/Updated Entire Document

08/15/2008	Revised/Updated Entire Document
06/15/2008	Revised/Updated Entire Document
03/15/2008	Revised/Updated Entire Document
05/01/2007	Revised/Updated Entire Document
12/01/2005	Revised/Updated Entire Document
02/01/2005	Revised/Updated Entire Document
07/30/2004	Revised/Updated Entire Document
12/01/2003	Revised/Updated Entire Document
05/01/2000	Revised/Updated Entire Document