BlueCross BlueShield of Alabama

Name of Policy:
TNF Antagonists and Other Biologics

Policy #: 061
Category: Pharmacy

Latest Review Date: October 2013
Policy Grade: A

Background/Definitions:

As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. *The technology must have final approval from the appropriate government regulatory bodies;*
2. *The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
3. *The technology must improve the net health outcome;*
4. *The technology must be as beneficial as any established alternatives;*
5. *The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. *In accordance with generally accepted standards of medical practice; and*
2. *Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
3. *Not primarily for the convenience of the patient, physician or other health care provider; and*
4. *Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.*

Description of Procedure or Service:

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

Remicade (infliximab) is a monoclonal antibody that binds with the human tumor necrosis factor alpha (TNFα) and is administered intravenously. Remicade reduces the infiltration of inflammatory cells and TNFα production in the inflamed areas of the intestines that occurs with Crohn's disease and is also approved for treatment of rheumatoid arthritis.

Cimzia (Certolizumab pegol) is a monoclonal antibody directed against tumor necrosis factor alpha (TNFα) and is administered by subcutaneous injection. Elevated levels of TNFα have been implicated in the pathology of Crohn's disease and rheumatoid arthritis. Certolizumab pegol binds to TNFα, inhibiting its role as a key mediator of inflammation.

Orencia (abatacept) is the first in a new class of drugs known as selective costimulation modulators. Orencia is indicated for reducing signs and symptoms, inducing major clinical response, slowing the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more disease modifying anti-rheumatic drugs (DMARDs), such as methotrexate or tumor necrosis factor (TNF) antagonists.

Actemra (tocilizumab) is a monoclonal antibody that binds to interleukin-6 (IL-6) in the body and blocks the effects of IL-6 in patients with rheumatoid arthritis and systemic juvenile idiopathic arthritis (SJIA) and is administered intravenously. Inflammation is the body's reaction to injury and is a necessary process for the repair of injury. IL-6 is a protein that the body produces when there is inflammation. The unchecked inflammation of rheumatoid arthritis and SJIA eventually leads to destruction of the joints. Tocilizumab binds to IL-6 in the body and thereby blocks the effects of IL-6. As a result, inflammation and its consequences in the joints are reduced, and the progressive destruction of the joints is slowed or prevented.

Stelara (ustekinumab) is the first of a new type of biologic for moderate to severe psoriasis that combines powerful psoriasis relief with very infrequent dosing and is administered by subcutaneous injection. Ustekinumab blocks interleukin-12 and interleukin-23, immune-system molecules that are believed to be inappropriately active in the skin and joints of people with psoriasis.

SIMPONI ARIA (golimumab) is an infusible, fully human anti-TNF monoclonal antibody that targets both soluble and transmembrane bioactive forms of TNF-alpha, a protein that when overproduced in the body due to chronic inflammatory diseases can cause inflammation and damage to bones, cartilage and tissue. By binding with and blocking TNF-alpha, SIMPONI ARIA helps control inflammation. SIMPONI ARIA also helps to inhibit the progression of further joint damage. SIMPONI ARIA is approved for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) with the medicine methotrexate.

Policy:
Remicade (infliximab)

Remicade (infliximab) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage for the following indications and criteria:

Fistulizing Crohn's Disease

- Treatment of **adult patients (18 years of age or older)** with fistulizing Crohn's disease for the reduction in the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure.
    - **Treatment:** In patients with fistulizing disease, an initial 5 mg/Kg should be followed by additional 5 mg/Kg doses at two and six weeks, followed by a maintenance regimen every eight weeks thereafter.

Crohn's Disease

- Treatment of **adult patients (18 years of age and older)** with moderately to severely active Crohn's disease for the reduction of signs and symptoms in patients who have had an inadequate response to conventional therapy. This can be classified as follows:
    - Crohn's disease on immunosuppressive therapies with activation or relapse of symptoms.
    - Crohn's disease currently on steroids with activation or relapse of symptoms that need to be placed on immunosuppressants. Remicade is given as a bridge until the immunosuppressive drugs can become effective.
    - Inability to tolerate drug therapy, i.e., pancreatitis from immunosuppressants, with activation or relapse of symptoms.
    - This would include diagnosis for enteritis associated with Crohn's disease.
    - **Treatment:** Intravenous administration of Remicade is 5 mg/Kg given as an induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/Kg every eight weeks thereafter for the treatment of moderately to severely active Crohn's disease. For patients who respond and then lose their response, consideration may be given to treatment up to 10 mg/Kg. Patients who do not respond by week 14 are unlikely to respond with continued dosing and consideration should be given to discontinue Remicade in these patients.
- Treatment of **pediatric patients** with moderately to severely active Crohn's disease for reduction of signs and symptoms in patients who have had an inadequate response to conventional therapy. **All** pediatric Crohn's disease patients must be up to date with all vaccinations prior to initiating Remicade therapy.

Rheumatoid Arthritis

- Treatment of **adult patients (18 years of age and older)** with a definitive diagnosis of rheumatoid arthritis who have tried at least one disease modifying anti-rheumatic drug (DMARD) for a combined period of at least six months with physician demonstrating an inadequate response to DMARD (see table below).
    - **Treatment:** Remicade is usually given in combination with methotrexate at 3mg/kg IV initial dosage followed by additional infusions at two and six weeks after the first infusions and repeated every eight weeks thereafter. For patients who have a response, consideration may be given to adjusting the dosage up to 10 mg/kg or treating as often as every four weeks.
    - A higher dosage or increase in administration frequency requires documentation of medical necessity for coverage (i.e., radiological data, physician/progress notes, patient clinical notes, medical literature, etc.).

DMARD drugs include the following:

Drug Class	Brand Name
Auranofin	Ridaura®
Aurothioglucose	Solganal®
Azathioprine	Imuran®
Cyclosporine	Neoral®
Gold sodium thiomalate	Aurolate®, Myochrysine®
Hydroxychloroquine sulfate	Plaquenil®
Leflunomide	Arava®
Methotrexate	Rheumatrex®
Penicillamine	Cuprimine®, Depen Titratable®
Sulfasalazine	Azulfidine®, Azulfidine EN-Tabs®

Ankylosing Spondylitis

- Treatment of patients who have had a diagnosis of Ankylosing Spondylitis for at least six months and have not had an adequate response to conventional therapy (i.e., NSAIDS, DMARDs or corticosteroids).
    - **Treatment:** Intravenous administration of Remicade is 5mg/kg given as an induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5mg/kg every six weeks thereafter for the treatment of active ankylosing spondylitis.

Psoriatic Arthropathy

- Treatment of patients who have had a diagnosis of Psoriatic Arthropathy for at least six months and have not had an adequate response to conventional therapy (i.e., NSAIDS, DMARDs or corticosteroids).
    - **Treatment:** Intravenous administration of Remicade is 5mg/kg given as an induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5mg/kg every eight weeks thereafter for the treatment of psoriatic arthritis. Remicade can be used with or without methotrexate.

Ulcerative Colitis

- Treatment of adult and pediatric patients with a diagnosis of chronic ulcerative colitis that have had inadequate response to conventional therapy (i.e., corticosteroids, t-aminosalicylates or 6-mercaptopurine). This is not first-line therapy, but a last resort before surgical intervention.
    - **Treatment:** Intravenous administration for Remicade is 5mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5mg/kg every eight weeks thereafter for the treatment of moderately to severely active ulcerative colitis.

Plaque Psoriasis

- Treatment of **adult patients (18 years of age or older)** with chronic severe (i.e. extensive and/or disabling) plaque psoriasis who are candidates for systemic therapy and when other therapies have been ineffective at controlling the disease (i.e., topical therapies like corticosteroids, phototherapy, and systemic therapy with methotrexate). Treatment beyond one year is not covered.

Use of Remicade for the treatment of guttate, pustular and erythrodermic psoriasis does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage.

Remicade (infliximab) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage **for off-label use or non-FDA approved labeled indications** for following diagnoses and criteria:

Behçet's Syndrome

- Must have documentation of diagnosis of disease, medications used and length of use (such as corticosteroids, e.g. prednisone; immunosuppressive therapy, e.g. azathioprine, chlorambucil, cyclosporine, methotrexate).
- Only be used after failure of other therapies (medications).
- Coverage for three month trial.
- Documentation of patient positive response to continue therapy after three months.

Takayasu's Arteritis

- Must have documentation that the patient is unresponsive to glucocorticoid therapy or cytotoxic drugs such as, but not limited to, cyclophosphamide, methotrexate, mycophenolate mofetil, and cyclosporine.

Wegener's Granulomatosis

- Must have documentation that the patient is refractory to standard treatment that includes but is not limited to: corticosteroids, cyclophosphamide, methotrexate (MTX) or azathioprine (AZA). These drugs generally produce remission in over 90% of affected people. Remicade is not first line therapy for this diagnosis.

Refractory Sarcoidosis

- Must have documentation that the patient is refractory to standard treatment. Corticosteroids are the mainstay of treatment, cytotoxic agents (such as; methotrexate and azathioprine (Imuran)) and immunomodulators (such as chloroquine (Aralen), hydroxychloroquine (Plaquenil), and cyclosporine).

Severe Hidradenitis Suppurativa

- Documentation of patient's condition with treatments and response to treatments to demonstrate failure or refractory status, may include but not limited to surgical treatments, Clorox baths, oral and topical antibiotics, etc.

Juvenile Idiopathic Arthritis

- Documentation that patient has tried and failed at least one disease modifying anti-rheumatic drugs (DMARD) for a combined period of at least three months. **(Effective 10/11/2012)**

Uveitis Refractory

- Documentation that patient has failed traditional treatment. **(Effective 10/11/2012)**

Actemra (tocilizumab)

Actemra (tocilizumab) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage for the following indications and criteria:

Rheumatoid Arthritis

Effective for dates of service on or after October 11, 2012:

- Treatment of **adult patients (18 years of age and older)** with a diagnosis of moderately to severely-active rheumatoid arthritis that have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDS).

Effective for dates of service on or after January 8, 2010 thru October 10, 2012:

- Treatment of **adult patients (18 years of age and older)** with a diagnosis of moderately to severely-active rheumatoid arthritis that have had an inadequate response to one or more TNF antagonist therapies. Treatment may be as monotherapy, with methotrexate or DMARDS.

Effective for dates of service on or after April 18, 2011:

- Treatment of **pediatric patients (2 years of age and older)** with systemic juvenile idiopathic arthritis (SJIA), also known as Still's Disease*.

***Juvenile rheumatoid arthritis alternative names include: juvenile chronic polyarthritis, JRA, Stills' disease, juvenile idiopathic arthritis. Source: Medline Plus-a service of the U.S. National Library of Medicine and the National Institutes of Health.**

Cimzia (certolizumab pegol)†

Cimzia (certolizumab pegol) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage for the following indications and criteria:

Crohn's Disease

- Treatment of **adult patients (18 years of age and older)** with a diagnosis of moderately to severely active Crohn's disease that have had an inadequate response to conventional therapy.

Rheumatoid Arthritis

- Treatment of **adult patients (18 years of age and older)** with active rheumatoid arthritis and have had an inadequate response to at least one disease modifying antirheumatic drug (DMARD).

Psoriatic Arthritis

- Treatment of **adult patients (18 years of age and older)** with active psoriatic arthritis. **(Effective 09/30/2013)**

Ankylosing Spondylitis

- Treatment of **adult patients (18 years of age and older)** with active ankylosing spondylitis. **(Effective 10/18/2013)**

†Cimzia 200 mg in lyophilized powder form is to be administered by a healthcare professional. Cimzia 200 mg in prefilled syringes is to be self-administered. Home Health services are not eligible for coverage for either form (self-injectable or lyophilized powder) of Cimzia.

Orencia (abatacept)†

Orencia (abatacept) meets Blue Cross and Blue Shield of Alabama's medical criteria for the coverage for the following indications and criteria:

Rheumatoid Arthritis

- Treatment of **adult patients (18 years of age and older)** with the diagnosis of moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more DMARDs, after a trial of at least six months or tumor necrosis factor (TNF) antagonists such as Remicade, Humira or Enbrel, etc.
- Treatment of **pediatric patients (6 years of age and older)** with the diagnosis of moderate to severe active polyarticular juvenile idiopathic arthritis*. It may be used as monotherapy or concomitantly with methotrexate.

†Orencia (abatacept) may be used as monotherapy or concomitantly with DMARDs other than TNF antagonists. Abatacept should not be administered concomitantly with TNF antagonists and is not recommended for use with anakinra (Kineret).

***Juvenile rheumatoid arthritis alternative names include: juvenile chronic polyarthritis, JRA, Stills' disease, juvenile idiopathic arthritis. Source: Medline Plus-a service of the U.S. National Library of Medicine and the National Institutes of Health.**

SIMPONI ARIA (golimumab)†

SIMPONI ARIA (golimumab) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage for the following indications and criteria:

Rheumatoid Arthritis

- Treatment of **adult patients (18 years of age or older)** with the diagnosis of moderately to severely active rheumatoid arthritis in combination with methotrexate.

†SIMPONI ARIA is prepared and administered intravenously by a healthcare professional every 8 weeks after 2 starter doses given 4 weeks apart. Home health services for the administration of SIMPONI ARIA are not covered.

Stelara (ustekinumab)†

Stelara (ustekinumab) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage for the following indications and criteria:

Plaque Psoriasis

- Treatment of **adult patients (18 years of age and older)** with the diagnosis of moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy; **and**
  - Must have a minimum involvement of 10% body surface area; **and**
  - Must have tried a DMARD or UVA light therapy with oral or topical psoralens (PUVA) for at least 6 consecutive months in the past year.

Psoriatic Arthritis

- Treatment of **adult patients (18 years of age and older)** with the diagnosis of moderate to severe psoriatic arthritis, alone or in combination with methotrexate. **(Effective 9/23/2013)**

†Stelara is administered via subcutaneous injection. Home health services for the administration of Stelara are not covered for a self-administered drug. Dosing is every 12 weeks after 2 starter doses given 4 weeks apart.

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member's contract and corporate medical policies. Physicians should always exercise their best

medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

Remicade (infliximab)

Tumor necrosis factor (TNF) is a cytokine produced by macrophages and T-cells. 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. Infliximab is administered via an IV infusion. Some precautions regarding the use of Remicade are testing for tuberculosis and avoiding treating if the patient has congestive heart failure. Warnings were issued in October 2001.

Current US Food and Drug Administration (FDA) labeled indications for Remicade include treatment of rheumatoid arthritis, fistulizing Crohn's disease, and moderately to severely active Crohn's disease that has had an inadequate response to conventional therapy. Elevated levels of TNF have been implicated in many inflammatory diseases, and there is now interest in expanding the use of infliximab to a variety of off-label indications. Among those off-label uses now included are Ankylosing Spondylosis and Psoriatic Arthritis.

On June 28, 2002, the FDA approved Remicade to reduce signs and symptoms, and induce and maintain clinical remission in patients with the following criteria: moderately to severely active Crohn's disease and an inadequate response to conventional therapy.

On April 3, 2003, the FDA approved marketing of Remicade for reducing the number of draining enterocutaneous and rectovaginal fistulas and for maintaining fistula closure in patients with fistulizing Crohn's disease. Approval was based on the results of the ACCENT II clinical trial assessing 54-week data on the effectiveness of maintenance therapy with Remicade in sustaining closure of draining fistulas in Crohn's disease.

Tumor Necrosis Factor Blocker Safety

A 2011 meta-analysis of 74 RCTs of TNF blockers found cancer was diagnosed in 0.84% (130/15,418) of patients randomized to TNF blocker treatment, whereas, 0.64% (48/7486) of patients randomized to comparator groups were diagnosed with cancer. However, this meta-analysis examined diagnosis of cancer in the short term, i.e., between the time period of starting TNF blocker treatment and 30 days after completed treatment. The need for long-term studies to further evaluate cancer risk with TNF treatment was noted. In a 2011 Cochrane meta-analysis and overview, 163 RCTs and 46 extension studies on biologics, totaling 61,964 patients, were evaluated for adverse effects. There was no statistically significant difference between biologics and comparators in the rate of serious adverse events including infection, lymphoma and heart failure. However, risk of withdrawal was significantly higher with infliximab than control (odds ratio [OR]: 2.04, 95% confidence interval [CI]: 1.43 to 2.91; number needed to harm=12, 95% CI: 8 to 28). The need for long-term studies to further evaluate the safety of biologics was also noted.

In 2012, a meta-analysis of lymphoma risk from tumor necrosis factor (TNF) blocker treatment was published by Wong and colleagues. The meta-analysis included 14 randomized controlled clinical trials (RCTs) and included 5,179 patients treated with TNF blockers and 2,306 controls. Lymphoma occurred in 11 patients treated with TNF blockers (0.21%), whereas four patients in the control groups (0.17%) developed hematolymphoid neoplasms; this was not statistically significant ($p<0.05$).

Ankylosing Spondylitis

Ankylosing Spondylitis is characterized by inflammation of the enthesis, the site where ligaments, tendons, and joint capsules insert into bone. Inflammation around the vertebrae, facet joints, and feet can lead to fibrosis, ossification, deformity, and ankylosis.

In studies on Spondylarthropathy by Brandt et al and Van den Bosch et al patient selection criteria included: to be at least 18 years of age, to have a negative pregnancy test, to have active disease and to be or have been taking disease modifying drugs. The study published on ankylosing spondylitis by Stone, et al, had inclusion criteria of active disease with information on prior drug history including use of DMARDS or corticosteroids. All studies demonstrated a decrease in disease manifestation. Long-term studies are not available other than one year. There has also been no determination of interval between dosing.

A 2007 systematic review examined the comparative clinical effectiveness and cost-effectiveness of adalimumab, etanercept, and infliximab for the treatment of ankylosing spondylitis. Nine placebo-controlled RCTs were included in the review of clinical effects. These included two studies of adalimumab, five of etanercept, and two of infliximab in comparison with placebo (along with conventional management). No RCTs directly comparing anti-TNF-alpha agents were identified. Meta-analyses were conducted for data on ASAS (20%, 50%, and 70% improvement, respectively), mean change in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), and mean change in Bath Ankylosing Spondylitis Functional Index (BASFI) at 12 weeks following initiation of anti-TNF-alpha therapy or placebo for all three drugs. Meta-analyses were also conducted at 24 weeks for etanercept and infliximab. Each meta-analysis of anti-TNF-alpha therapy demonstrated statistically significant advantages over placebo, although there was no significant difference between individual anti-TNF-alpha agents. At 12 weeks, ASAS 50% responses were 3.6-fold more likely with anti-TNF-alpha treatment than placebo. Compared with baseline, BASDAI scores were reduced by close to two points at 12 weeks. Functional scores (BASFI) were reduced at 12 weeks. Six full economic evaluations (two peer-reviewed published papers, four abstracts) were included in the review. The conclusions among economic evaluations were mixed, although the balance of evidence indicates that over short timeframes anti-TNF-alpha therapies are unlikely to be considered cost-effective. The limitations of the clinical outcome data impose restrictions on the economic assessment of cost-effectiveness. Direct unbiased randomized controlled trial evidence is only available in the short term. Current assessment tools are limited and, at present, BASDAI and BASFI are the best available, although not designed for, or ideal for, use in economic evaluations. The review of the three models submitted to National Institute for Health and Clinical Excellence (NICE) identified a number of inherent flaws and errors. The incremental cost-effectiveness ratios (ICERs) of etanercept and adalimumab were roughly similar, falling below an assumed willingness-to-pay threshold of 30,000 pounds. The ICER for infliximab was in the range of 40,000–50,000 pounds

per quality-adjusted life-year (QALY). The short-term (12-month) model developed by this report's authors confirmed the large front-loading of costs with a result that none of the three anti-TNF-alpha agents appears cost effective at the current acceptable threshold, with infliximab yielding much poorer economic results (57,000–120,000 pounds per QALY). The assumptions of the short-term model were used to explore the cost-effectiveness of the use of anti-TNF-alpha agents in the long term.

In 2012, Migliore and colleagues conducted a systematic review and Bayesian mixed treatment comparison of the effects of TNF alpha-blockers (infliximab, etanercept, and adalimumab) for the treatment of ankylosing spondylitis. Included in the comparison were three RCTs that evaluated Assessment in Ankylosing Spondylitis (ASAS) response criteria. All three TNFs examined were found to be more effective than placebo in achieving ASAS 20. However, infliximab was found to have an approximately seven times greater probability of treatment response (OR: 6.8) compared to etanercept (5 five times; OR: 4.9) or adalimumab (four times; OR: 4.4). Limitations to this analysis include few available studies, differences in study designs, and a fixed comparison model.

In 2013, Machado and colleagues performed a meta-analysis of RCTs to evaluate the efficacy and safety of the various anti-TNF agents for the treatment of ankylosing spondylitis. The primary outcome was the ASAS 20 response, which is defined by the Assessment of SpondyloArthritis international Society (ASAS) as a reduction by at least 20 % and 10 units (visual analog scale from 0 to 100) in at least three of the following domains: patient global assessment lumbar pain, physical function, and inflammation (without a worsening of >20 % and 10 units in the remaining fourth domain). Seven (of 18) trials included in this review (published through September 2012) assessed the effects of infliximab; five of infliximab with placebo, one of infliximab and methotrexate versus methotrexate and placebo, and one of infliximab versus etanercept. Under subgroup analyses, at 12/14 weeks, the golimumab presented the highest relative risk (RR) for ASAS 20 response (2.74, 95% confidence interval (CI) 1.78-4.22), followed by adalimumab (RR, 2.33; 95% CI, 1.45-3.74), etanercept (RR, 2.13; 95% CI, 1.75-2.58), and infliximab (RR, 1.82; 95% CI, 1.16-2.58). After 24 weeks, only one study of each anti-TNF agent remained in the meta-analysis and the highest RR was related to infliximab (RR, 3.18; 95% CI, 1.99-5.08), followed by etanercept (RR, 2.53; 95% CI, 1.80-3.57) and adalimumab (RR, 2.15; 95% CI, 0.96-4.83). The incidence of adverse events was not significantly different between the groups.

Significantly higher rates for ASAS 20 response (as with other outcome measures) was also reported with anti-TNF agents compared to placebo in another meta-analysis published in 2013 by Ren and colleagues, with most adverse events in both treatment groups being of mild or moderate in severity. It is important to consider the limitations of the included trials in both systematic reviews, especially in regard to investigating rare adverse events that were not the primary outcome of any study. These limitations are mainly the result of three factors: small sample sizes, short follow-up periods, and selection criteria that exclude patients with recent infections, a history of neoplasms, and significant comorbidities.

In conclusion, the review of clinical data related to the three drugs (including conventional treatment) compared with conventional treatment plus placebo indicates that in the short term

(12–24 weeks), the three treatments (adalimumab, etanercept, and infliximab) are clinically effective in relation to assessment of ASAS, BASDAI, and BASFI. Indirect comparisons of treatments were limited and did not show a significant difference in effectiveness between the three agents. The short-term economic assessment indicates that none of the three anti-TNF-alpha agents is likely to be considered cost-effective at current acceptability thresholds, with infliximab consistently the least favorable option.

Behçet's Syndrome

Behçet's Syndrome is a chronic, relapsing, inflammatory disorder with mucocutaneous, ocular, articular, vascular, gastrointestinal, and central nervous system. The four most common symptoms are mouth sores, genital sores, inflammation inside of the eye, and skin problems. Other symptoms may include arthritis, blood clots, and inflammation in the central nervous system and digestive organs.

A number of studies are referred to in a literature review supplied by the manufacturer. Most studies are performed with few participants. Most recipients of the treatments had an immediate response of greatly improved oral and genital ulcers, decrease in eye inflammation, skin lesions or retinal lesions. Most dosing was at 5 mg/kg at an average of 0, 2, and 6 weeks. Most authors concluded that Remicade may be beneficial in inducing remission in patients with Behçet's disease.

Crohn's Disease

A 2011 systematic review of 11 RCTs of infliximab and adalimumab for the treatment of Crohn's disease (CD) found both agents improved outcomes in moderate to severe and fistulizing Crohn's disease compared to placebo. A multicenter open-label randomized controlled trial (RCT) from Europe of 133 patients with active CD who had not been previously treated with corticosteroids, antimetabolites, or biological agents and who were assigned either early combined immunosuppression (infliximab plus either azathioprine or methotrexate) or conventional management (induction with corticosteroids and sequentially adding antimetabolites [azathioprine or methotrexate] and infliximab) with two-year follow-up, found that early immunosuppression was more effective than conventional therapy for preventing disease progression. At 26 weeks, 60% versus 36% of the early immunosuppression and conventional treatment groups were in remission (remission rates were statistically different at one year [62% and 42%, respectively] but not at two years). Corticosteroid, but not antimetabolite, usage was lower, and the median time to relapse was longer in the early immunosuppression group (329 days vs. 175 days). Safety profiles were similar, although the study was not powered to detect safety differences. In 2010, results of the randomized, double-blind SONIC trial were reported. In the SONIC trial, 508 adult patients with moderate to severe Crohn's disease received either infliximab monotherapy, azathioprine monotherapy, or a combination of these two drugs. At week 26, corticosteroid-free clinical remission was achieved in 56.8% (96/169) of combination therapy patients, 44.4% (75/169) of infliximab monotherapy patients ($p=0.02$), and 30.0% (51/170) of azathioprine monotherapy patients (comparison with combination therapy $p<0.001$; and comparison with infliximab $p=0.006$). At week 50, numerical trends were similar. Mucosal healing at week 26 had occurred in 43.9% (47/107) of combination therapy patients, 30.1% (28/93) of infliximab patients ($p=0.06$), and 16.5% (18/109) of

azathioprine patients (comparison with combination therapy p<0.001, comparison with infliximab p=0.02).

A systematic review examined the evidence for the effectiveness of TNF-alpha blocking agents in the maintenance of remission in patients with CD refractory to conventional treatments, including corticosteroids and immunosuppressants. In the reviewed RCTs, patients older than 18 years with CD who had a clinical response or clinical remission with a TNF-alpha blocking agent, or patients with CD in remission but unable to wean corticosteroids, were randomized to maintenance of remission with a TNF-alpha blocking agent or placebo. Outcome measures reported in the primary studies included clinical remission, clinical response, and steroid-sparing effects. Nine studies met all inclusion criteria. Pooled results from three RCTs found that infliximab maintains clinical remission (risk ratio [RR]: 2.50; 95% CI: 1.64 to 3.80), clinical response (RR: 2.19; 95% CI: 1.27 to 3.75), fistula healing (RR: 1.87; 95% CI: 1.15 to 3.04) and has corticosteroid-sparing effects (RR: 3.13; 95% CI: 1.25 to 7.8), in patients with CD responsive to infliximab induction therapy. There is evidence from two randomized controlled trials that adalimumab maintains clinical remission to week 54 (RR: 3.28; 95% CI: 2.13 to 5.06), has higher rates of steroid-free remission at week 26 and week 56 versus placebo (6% placebo, versus 29% adalimumab), and is superior to placebo for maintenance of steroid-free remission to week 54 (RR: 4.24; 95% CI: 1.57 to 11.47). There was evidence from one randomized controlled trial comparing certolizumab pegol to placebo, which found certolizumab pegol to be effective for maintenance of clinical remission (RR: 1.68; 95% CI: 1.30 to 2.16) and clinical response (RR: 1.74; 95% CI: 1.41 to 2.13) to week 26.

The authors concluded infliximab 5 mg/kg or 10 mg/kg, given every eight weeks, is effective for the maintenance of remission and maintenance of fistula healing in patients who have responded to infliximab induction therapy. Adalimumab, 40 mg weekly or every other week, is effective for the maintenance of remission in patients who have responded to adalimumab induction therapy. Certolizumab pegol, 400 mg every four weeks, is effective for the maintenance of remission in patients who have responded to certolizumab induction therapy. No comparative trials have evaluated the relative efficacy of these agents. Adverse events are similar in the infliximab, adalimumab, and certolizumab groups compared with placebo, but study size and duration generally are insufficient to allow an adequate assessment of serious adverse events associated with long-term use.

A review article examined the evidence base of both established treatments (such as enteral nutrition, corticosteroids, 5-aminosalicylates, and immunosuppressive agents) and emerging treatments (such as the anti-tumor necrosis factor-alpha agents, infliximab and adalimumab) used to induce and maintain remission in CD. The authors conclude exclusive enteral nutrition is recommended as the first-line of treatment for the induction of remission in pediatric CD. Corticosteroids are also effective for inducing remission but may be associated with significant adverse events. Patients with chronically active CD may benefit from immunosuppressive agents such as azathioprine and methotrexate. Infliximab is effective for inducing remission in patients who continue to have significant active disease despite the use of conventional treatments. Adalimumab may be indicated for patients who develop a severe allergic reaction to infliximab or those who initially respond to infliximab but subsequently lose their response. Treatments that have been shown to be effective for the maintenance of remission include azathioprine,

methotrexate, infliximab, and adalimumab. Recent evidence also suggests that long-term enteral nutritional supplementation with patients taking about half of their daily calorie requirements as enteral nutrition may be an effective strategy for the maintenance of remission in CD.

A meta-analysis examined placebo-controlled trials to evaluate safety and efficacy of TNF antagonists for CD. The primary endpoints were clinical remission for luminal CD and fistula closure at greater than or equal to two consecutive visits. Ten studies evaluated anti-TNF treatment of fistulizing CD, involving 776 patients. In overall analysis, anti-TNF therapy was effective for fistula closure only in maintenance trials after open-label induction (mean difference, 16%; 95% CI: 8-25%; $p<0.001$). In 21 studies enrolling 5,356 individuals, anti-TNF therapy did not increase the risk of death, malignancy, or serious infection. The authors concluded infliximab, adalimumab, and certolizumab are effective in luminal CD. Efficacy of anti-TNF agents other than infliximab in treating fistulizing CD requires additional investigations. A longer duration of follow-up and a larger number of patients are required to better assess the safety profile of TNF antagonists in CD.

A review article explored conventional and emerging treatments for CD and ulcerative colitis. The authors discuss 5-aminosalycylic acid agents (mesalamine, olsalazine) a mainstay in the treatment of both CD and ulcerative colitis. Antibiotics may have a limited role in the treatment of colonic CD. Steroids continue to be the first choice to treat active disease not responsive to other more conservative therapy. Non-systemic steroids such as oral and rectal budesonide for ileal and right-sided CD and distal ulcerative colitis, respectively, are also effective in mild-moderate disease. 6-mercaptopurine and its pro-drug azathioprine are steroid-sparing immunomodulators, effective in the maintenance of remission of both CD and ulcerative colitis, while methotrexate may be used in both induction and maintenance of CD. Infliximab and adalimumab are anti-TNF agents approved in the United States and Europe for the treatment of CD, and infliximab is also approved for the treatment of ulcerative colitis.

A systematic review and meta-analysis of infliximab treatment given preoperatively to patients with Crohn’s disease (CD) was published in 2012 by Kopylov et al. This review found an increase in postoperative infections associated with preoperative infliximab and “a trend toward an increased risk of noninfectious and overall complications.” In another systematic review and meta-analysis in 2011, Ehteshami-Afshar and colleagues also found an increase in postoperative infections in patients using infliximab for inflammatory bowel disease. Pouch-related complications, sepsis and thrombotic events were also more common in patients using infliximab. However, as the reviewers noted, patients receiving infliximab usually have more severe disease and have been refractory to other treatments, thereby, possibly being more susceptible to increased complications.

Several studies have reported on the use of infliximab for pediatric CD. In the REACH trial, 112 children, age 6-17 years, with severe CD [Pediatric Crohn's Disease Activity Index (PCDAI) score >30] that responded inadequately to standard therapy were given infliximab intravenous therapy. Those patients that responded to infliximab therapy at 10 weeks were randomized to 5mg/kg every 8 or 12 weeks. After 10 weeks of treatment, 88.4% (99/112) of patients responded to infliximab, and 58.9% (66/112) of patients reached clinical remission. After 54 weeks of treatment, clinical remission was achieved in more patients on an eight-week infliximab schedule

than compared to a 12-week schedule [55.8% (29/52) vs. 23.5% (12/51), respectively]. At 46 weeks, 60 patients continued infliximab treatment for three more years in the open-label extension trial. Infliximab was effective in decreasing disease activity to no disease or mild disease in approximately 80% of patients. Serious infection occurred in 10% (6 patients).

In 2013, Rosenfeld and colleagues published a meta-analysis of studies comparing the rates of post-operative complications among CD patients treated with Infliximab therapy versus alternative therapies. Data were extracted from six observational studies (published through October 2012) including 1159 patients among whom 413 complications were identified. The most common complications were wound infections, anastomotic leak and sepsis. There was no significant difference in the major complication rate (OR, 1.59; 95% CI, 0.89–2.86; p = 0.15), minor complication rate (OR, 1.80; 95% CI, 0.87–3.71; p = 0.11), reoperation rate (OR, 1.33; 95% CI, 0.55–3.20; p = 0.52) or 30-day mortality rate (OR, 3.74; 95% CI, 0.56–25.16; p = 0.13) between the infliximab and control groups. Key limitations of this meta-analysis included a high degree of heterogeneity in the analyses of major complication rates given the observational study designs. In addition, the included studies varied in terms of severity, location and duration of disease, as well as the type of surgical procedure, whether it looked at single or multiple surgical procedures and the method (laparoscopic or open) of surgery.

In 2013, Yoshida and colleagues published a prospective, Japanese single-center, RCT to assess the efficacy of scheduled maintenance infliximab monotherapy to prevent postoperative CD recurrence. Thirty-one CD patients who had ileocolic resection within the past four weeks were randomly assigned to scheduled infliximab at 5 mg/kg intravenously every eight weeks for 36 months (n=15) or without infliximab (control arm on conventional medication (if any), n=16). All patients were treated without immunomodulator or corticosteroid following surgery. The primary and secondary endpoints were remission rates at 12 and 36 months, defined as CD Activity Index (CDAI) ≤ 150, an International Organization for the Study of Inflammatory Bowel Disease (IOIBD) score <2, and C-reactive protein (CRP) <0.3 mg/dL. Additionally, endoscopic recurrences at 12 and 36 months were evaluated. At 12 and 36 months, 100%, and 93% of patients in the infliximab group were in remission (IOIBD <2), respectively vs. 69% and 56% in the control arm (p < 0.03). Similarly, 87% and 87% of patients in the IFX group maintained serological remission (CRP <0.3 mg/dL) versus 37.5% and 37.5% in the control arm (p < 0.02). In addition, the infliximab group achieved higher endoscopic remission at 12 months, 79% versus 19% (p = 0.004). However, in the Kaplan–Meier survival analysis the CDAI scores between the two arms were not significantly different either at 12 or at 36 months. No adverse events were observed. Future multi-center trials in larger cohorts of patients and over a longer time period need to be undertaken to confirm these findings

In conclusion, the clinical data related to the use of TNF-blocking agents in the treatment of CD indicates that infliximab, adalimumab, and certolizumab pegol are effective for the maintenance of remission in patients who have responded to induction therapy. The efficacy of anti-TNF agents, other than infliximab, in treating fistulizing CD requires additional investigation. Studies with longer duration of follow-up and larger number of patients are required to better assess the long-term safety profile of TNF antagonists in CD.

Hidradenitis Suppurativa (HS)

Hidradenitis suppurativa is a chronic inflammatory skin disease characterized by abscess formation, predominantly in the axillae and groin. The disorder is difficult to treat and has a severe impact on quality of life. Early studies for the use of infliximab were small but promising. More recently some studies are getting longer follow-up and more participants. Mekkes and Bos (2008) reported on 10 patients with severe, recalcitrant hidradenitis and were treated with infliximab and were followed for at least a year. All patients improved within two to six weeks. Three patients had long-lasting improvement, with no recurrence of lesions in a two-year follow-up period. The other patients showed recurrence of lesions after 8.5 months. The authors concluded that infliximab was effective in severe hidradenitis suppurativa, leading to a reduction of symptoms for a prolonged period. Grant et al (2010) conducted a prospective, double-blind study involving 38 patients that received either placebo or infliximab. More patients in the infliximab than in the placebo group showed a 50% or greater decrease from baseline HS Severity Index score. Patients in the placebo group treated with infliximab after week eight (crossover) responded similarly to the original infliximab group. In conclusion, the authors stated that infliximab was well tolerated, no unexpected safety issues were identified, and improvements in pain intensity, disease severity, and quality of life were demonstrated with concomitant reduction in clinical markers of inflammations.

Inflammatory Bowel Disease

In 2013, Costa and colleagues published a meta-analysis on the rates of hospitalizations and surgery in patients with inflammatory bowel disease treated with infliximab (Crohn's disease (CD) and ulcerative colitis (UC). Twenty-seven eligible studies (published through May 2012) were included (nine RCTs and 18 observational studies). Overall, 1,912 patients were evaluated in these trials (1,076 with CD, and 836 with UC). Infliximab treatment was associated with a significant odds reduction of hospitalization risk in comparison to controls, both in RCTs (OR, 0.51; 95% CI, 0.40–0.65; I2 test for heterogeneity = 0%) and observational studies (OR, 0.29; 95% CI, 0.19–0.43; I2 = 87%). The magnitude of this risk reduction was similar across patients with CD and UC. In patients with CD, the RCTs and observational findings on overall major surgery rate were consistent. Infliximab treatment was associated with a significant odds reduction of overall major surgery risk in comparison to controls, in both RCTs (OR, 0.31; 95% CI, 0.15–0.64; I2 = 0%) and observational studies (OR, 0.32; 95% CI, 0.21–0.49; I2 = 77%). In patients with UC, pooled results from RCTs and observational studies on overall major surgery rate were different. Infliximab treatment was associated with a significant 43% odds reduction of overall major surgery risk in RCTs (OR, 0.57; 95% CI, 0.37–0.88; I2 = 0%); on the other hand, a non-significant increase was found in pooled results from observational studies (OR, 1.43; 95% CI, 0.65–3.13; I2 = 76%). There were several limitations with this meta-analysis including potential selective reporting and failure to describe withdrawals (attrition bias) in the included RCTs, and presentation of unadjusted risk estimates in observational studies. In addition, there was significant heterogeneity in the findings from observational studies, and three (of 18) studies were published in abstract form.

In 2012, Lichtenstein and colleagues published a pooled analysis on the safety of long-term infliximab treatment, with/without concomitant immunomodulators, for CD and UC across 10 industry-sponsored studies. These studies included five RCTs contributing data from patients who received intravenous infliximab 5 or 10 mg /kg (n=1,713; ± azathioprine) or placebo (n=

406; ± azathioprine). No significant increase in infections, serious infections, or malignancy with infliximab versus placebo was reported in patients with inflammatory bowel disease. For example, when expressed on the basis of incidence (95% CI) per 100 patient-years of follow-up, overlapping 95% CIs indicated that the incidences of malignancies were similar in the placebo- and infliximab-treated patients with CD (1.61 (0.19-5.82) vs. 0.49 (0.18-1.06), respectively) and with UC (0.00-1.43) vs. 0.60 (0.20-1.40), respectively).

Juvenile Idiopathic Arthritis

In August 2011, the Agency for Healthcare Research and Quality (AHRQ) published a Comparative Effectiveness Review of disease-modifying anti-rheumatic drugs (DMARDs) for children with juvenile idiopathic arthritis (JIA). The review found available evidence on biologic DMARDs is limited although symptom improvement has been reported. Heterogeneous studies and reporting of outcomes, as well as varied categories of JIA make meaningful comparisons of DMARDs difficult. Additionally, many questions remain regarding the safety of DMARDs in children, especially since there is a risk of malignancy, particularly lymphoma, with the use of TNF-alpha blocking agents.

Ruperto and colleagues reported on an open-label extension trial of infliximab for juvenile idiopathic arthritis in 78 children. However, this study is limited by the high number of patients who discontinued infliximab treatment (42 patients) for various reasons. Of the remaining 36 patients, 40% achieved American College of Rheumatology (ACR)-Pedi 50 response criteria at week 204, whereas 33% achieved ACR-Pedi 70 during this time period. Inactive disease status was achieved in 13% of patients.

In a 2011 report of a multi-center, 54-week, randomized, open-label trial of 60 patients with juvenile idiopathic arthritis, by Tynjala, et al, infliximab plus methotrexate was found to result in better outcomes than methotrexate alone or in a combination of methotrexate, sulfasalazine, and hydroxychloroquine. In patients receiving TNF, 100% (19/19) achieved ACR-Pedi 75 compared to 65% (13/20) on combination treatment and 50% (10/20) on methotrexate. Inactive disease status was achieved in 13 TNF patients versus eight and five in the combination and methotrexate groups, respectively. Inactive disease also continued for a longer duration in the TNF group compared to the combination and methotrexate groups (mean 26 weeks versus 13 weeks and 6 weeks, respectively). A 2010 evidence-based review notes that infliximab is frequently used to treat JIA in clinical practice despite not having FDA approval for this indication.

Plaque Psoriasis and Psoriatic Arthritis

Psoriatic skin lesions are associated with increased local concentrations of tumor necrosis factor. This observation plus the association with psoriatic arthritis forms the rationale for the use of infliximab

In 2012, the Agency for Healthcare Research and Quality (AHRQ) issued an update of its 2007 report on drug therapy for adult psoriatic arthritis. The review found available evidence on biologic DMARDs is limited, although symptom improvement has been reported. The reviewers noted firm conclusions could not be drawn about the comparative efficacy, effectiveness, functional status, health-related quality of life, or tolerability of DMARDs, including infliximab.

In 2011, a systematic review of infliximab, etanercept or adalimumab for psoriasis concluded each of these three agents was effective in reducing skin disease and joint symptoms. Synthesis of the evidence found infliximab was more effective in improving skin and joint outcomes over etanercept and adalimumab. In another 2011 systematic review and meta-analysis, the risk of infections and lymphoma from TNF blocker treatment for psoriatic disease was examined from 20 studies. The risk of overall infection was odds ratio (OR): 1.18 (95% CI: 1.05-1.33). The risk of serious infection was OR: 0.70 (95% CI: 0.40-1.21). Malignancy OR was 1.48 (95% CI: 0.71-3.09).

Randomized controlled trials comparing the effectiveness of TNF alpha-blocking agents for psoriatic arthritis are lacking. Migliore and colleagues conducted a mixed treatment comparison analysis of etanercept, infliximab, and adalimumab and found the greatest ACR 20 response compared to placebo occurred with etanercept. In a systematic review and meta-analysis in 2012, Reich and colleagues compared biologics available in Europe for the treatment of moderate to severe psoriasis in adults. Included in the analysis were four RCTs on infliximab. Using Bayesian methods to estimate comparative effectiveness, the highest predicted mean probability of response occurred with infliximab at psoriasis area and severity index (PASI) levels 50 (93%), 75 (80%), and 90 (54%), followed by ustekinumab 90 mg, ustekinumab 45 mg, adalimumab, etanercept and efalizumab. In another 2012 systematic review and meta-analysis, Lucka, et al found infliximab and ustekinumab were most effective over a 24-week treatment period followed by adalimumab and etanercept. The effectiveness of infliximab, adalimumab, and etanercept decreased after 24 weeks. However, these analyses are limited by the use of indirect comparisons.

The infliximab multinational psoriatic arthritis controlled trial (IMPACT) was a randomized study of infliximab as a treatment of psoriatic arthritis. A secondary outcome focused on improvements in dermatologic manifestations of psoriasis. A total of 104 patients with psoriatic arthritis participated in this randomized, placebo-controlled and blinded study. Of these, only 39 had significant psoriatic skin lesions, as evidenced by a PASI score of equal to or greater than 2.5. (The maximum PASI score is 72. The score reflects lesional erythema, scaling, and thickness in four anatomic areas.) Patients received infliximab or placebo at 0, 2, 6, and 14 weeks. After week 16, patients initially assigned to receive placebo crossed over to receive infliximab every eight weeks through week 50, while patients randomized to infliximab continued to receive active treatment. Changes in the PASI score were analyzed for the 39 patients with skin lesions; 68% of infliximab patients achieved improvement of equal to or greater than 75% in the PASI score at week 16 compared to none in the placebo group. However, interpretation of these results is limited. The sample size was only 39 patients. In addition, patients were recruited to this trial based on arthritic manifestations with previous failure of one or more disease-modifying anti-rheumatic drugs (DMARDs). In contrast, it is not known whether previous therapies had been successful in controlling dermatologic manifestations of psoriasis.

Gottlieb and colleagues reported on a larger trial of 249 patients with severe plaque psoriasis who were randomized to receive an infusion of one of two different doses of infliximab or placebo at 0, 2, and 6 weeks. In contrast to the IMPACT study, which enrolled patients with a

PASI score of equal to or greater than 2.5, this study was limited to patients with a PASI score of 12 or greater and with psoriatic plaques covering at least 10% of their body surface. The primary endpoint was the proportion of patients who achieved at least 75% improvement in the PASI score from baseline at week 10. At week 10, 72% of patients treated with infliximab (3 mg/kg) and 88% of patients treated with infliximab (5 mg/kg) achieved a 75% or greater improvement from baseline in the PASI score, compared to 6% in the placebo group ($p<0.001$). While no studies directly compared various agents, these positive results were considered similar to that associated with cyclosporine, better than that associated with etanercept (another anti-TNF), and better than other topical agents. Results from this larger trial demonstrated that infliximab is an effective alternative in patients with moderately severe psoriasis who meet study criteria.

In 2010, Atteno and colleagues reported on a randomized trial of 100 patients treated with infliximab, etanercept, or adalimumab for psoriatic arthritis. All three agents were effective in controlling signs and symptoms of psoriatic arthritis at 12 months.

In 2012, Baranauskaite et al reported on a randomized, open-label study comparing infliximab with methotrexate to infliximab alone in 115 patients with psoriatic arthritis in the RESPOND study. Infliximab with methotrexate resulted in greater improvements in outcomes and disease suppression than methotrexate alone. In the intention-to-treat analysis at 16 weeks, 44 of 51 patients (86.3%) achieved an American College of Rheumatology (ACR) 20 response on infliximab with methotrexate versus 32 of 48 patients (66.7%) in the methotrexate only group. ($p=0.021$). ACR 50 and ACR 70 responses were also significantly greater in the combination treatment group. Improvements in PASI scores were also statistically significantly greater at each time point in the combination treatment group. The mean reduction in PASI score by 16 weeks was 93.3% in the combination group and 67.4% in the methotrexate only group ($p=0.0029$). While adverse events were higher in the combination group, most adverse events were considered to be mild to moderate. Barker and colleagues reported on a randomized, open-label study of infliximab versus methotrexate in 868 methotrexate-naïve patients with moderate-to-severe plaque psoriasis in the RESTORE1 study. At 16 weeks, significantly more patients achieved PASI 75 in the infliximab-treated group (508/653, 78%) than the methotrexate group (90/215, 42%; $p<0{\cdot}001$).

In 2012, the Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review to examine the benefits and harms of anti-TNF/biologic systemic agents compared with non-biologic systemic agents or phototherapy in patients with chronic plaque psoriasis. In total, five RCTs (n=1,227) and four observational studies (n=1,066) published through June 2012 were included in the AHRQ review. These studies directly compared either a systemic biologic agent with a systemic non-biologic agent or phototherapy and reported at least one outcome of interest. Five RCTs (two good, two fair, and one poor quality) and two fair-quality observational studies evaluated the comparative effectiveness of systemic biologic agents and systemic non-biologic agents. The comparisons made included adalimumab, etanercept, infliximab, and ustekinumab versus methotrexate and etanercept versus acitretin. The comparative effectiveness of these therapies with regard to final health outcomes other than health-related quality-of-life (HRQoL) could not be determined because of a lack of evaluation in the included literature. When comparing infliximab with methotrexate, HRQoL was improved in patients taking infliximab, based on a single RCT (low strength of evidence). There was

insufficient evidence to evaluate myocardial infarction and diabetes mellitus, and no other final health outcomes were reported. The evidence-base for the comparative safety of systemic biologic agents and systemic non-biologic agents or phototherapy was sparse. Overall five RCTs (two good, two fair, and one poor quality) and two observational studies (both fair quality) directly compared biologics with non-biologics and reported at least one adverse outcome of interest; there were no studies which directly compared infliximab with other biologics/agents in the evaluation of harms. Additional RCTs or large observational studies and registries that directly compare individual drugs/interventions across these agents are needed to further examine the benefits and harms of these agents for treatment in patients with chronic plaque psoriasis. These trials should be adequately powered to assess final health outcomes that are important to decision makers, such as mortality, major adverse cardiovascular events, and psychological outcomes. Future analyses using indirect comparisons may also help supplement lack of direct comparative data.

In 2013, two systematic reviews were published to assess the effectiveness and safety of anti-TNF agents in the treatment of psoriatic arthritis. These reviews reported no significant differences in effectiveness and overall adverse reactions between the available anti-TNF agents in patients with psoriatic arthritis.

Rheumatoid Arthritis

Many studies have been published demonstrating that TNF blockers, including infliximab, are more effective than placebo for the treatment of rheumatoid arthritis (RA). In 2013, Callhoff and colleagues published a meta-analysis to estimate the impact of biologic agents on physical function in patients with RA. Thirty-five RCTs were included in the analysis, 10 with DMARD-naive patients and 25 with DMARD IRs. These studies contained 43 biologic treatment arms were included in the analysis. Among the 43 treatment arms there were five with abatacept, 15 with adalimumab, three with certolizumab, seven with etanercept, four with golimumab, five with infliximab and four with rituximab. Overall, biologics led to a greater improvement of physical function than non-biologic DMARDs, with a standardized mean difference of the Health Assessment Questionnaire of 0.44 (95% CI, 0.38-0.50). There were no significant differences between individual biologics in both groups.

In 2012, Lopez-Olivo and colleagues published a meta-analysis evaluating the risk of developing any type of malignancy in patients with RA only and providing data on nine approved anti-TNF agents (including infliximab). The use of these agents among RA patients included in a pooled analysis of 63 RCTs (published through July 2012) of at least 6 months' duration was not significantly associated with an increased risk of malignancy compared with other DMARDs or with placebo. Of the 29,423 patients, 211 developed a malignancy during the trial (118 solid tumors, 48 skin cancers, 14 lymphomas, 5 hematologic nonlymphomas, and 26 not specified). Another meta-analysis of 33 RCTs published in 2012 by Moulis and colleagues similarly did not find any evidence for an increased cancer risk on five anti-TNF agents (including infliximab) in adult RA patients during up to two years of treatment.

In April 2012, the Agency for Healthcare Research and Quality (AHRQ) published an update to its 2007 Comparative Effectiveness Review on RA drug therapy and found comparative studies on biologic DMARDs are limited. While there are many observational comparative studies and

mixed treatment comparisons (MTCs), studies have not provided sufficient evidence to determine appropriate strategies for use of biologic DMARDs, such as infliximab, including when to begin biologic DMARDs and in what drug therapy combinations. Superiority of any biologic DMARD over others could not be determined due to the lack of head-to-head trials comparing biologic DMARDs. Only one head-to-head randomized controlled trial by Schiff and colleagues was identified for the AHRQ review. In this trial, in which abatacept and infliximab were compared to placebo, disease activity decreased more with abatacept, but remission was not significant at one year, as measured by the Disease Activity Score (DAS). The other seven trials included in the AHRQ review on biologic DMARDs were not randomized. Efficacy appeared to be similar among biologic DMARDs, except for Anakinra, which was found to be less effective. Additionally, etanercept may result in greater treatment outcome improvements in disease activity, but the evidence was considered to be of low strength, which limits interpretation of the MTC meta-analysis. Tolerability of biologic DMARDs was similar overall; however, cohort studies reported heart failure risk increased with biologic DMARDS, including infliximab.

In two systematic reviews and meta-analyses in 2012 (Gallego-Galisteo and Aaltonen), no TNF blocker produced superior outcomes in the treatment of RA. In Aaltonen et al, TNF blockers were found to have comparable outcomes to methotrexate, but when used together, outcomes were superior to when methotrexate or TNF blockers were used alone.

In another 2012 systematic review by Schmitz and colleagues comparing TNF blockers for the treatment of RA using a Bayesian mixed treatment comparison (MTC), etanercept and certolizumab were estimated to be more efficacious than infliximab. Additionally, adalimumab, certolizumab, etanercept and golimumab resulted in better Health Assessment Questionnaire outcomes than infliximab. The authors noted limitations in interpreting results with the MTC approach. A similar 2011 review by Turkstra et al, using an MTC approach, suggests etanercept and certolizumab may be more effective than abatacept, adalimumab, anakinra, golimumab, infliximab, rituximab, and tocilizumab for RA treatment.

A systematic review by Malottki et al, in 2011, discussed adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of RA after failed treatment with a TNF blocker. The reviewers found the evidence suggested rituximab and abatacept were more effective than supportive care. However, data on clinical effectiveness and comparisons of these TNF blockers is limited. Additionally, the benefits of using an alternative TNF blocker after failed first TNF blocker are uncertain.

In 2009, a review of six Cochrane reviews, including data from four studies on infliximab, was conducted to compare the safety and efficacy of abatacept, adalimumab, anakinra, etanercept, infliximab, and rituximab for RA. Based on indirect comparisons, all of the biologics were similarly efficacious on the primary outcome measure of American College of Rheumatology 50 score, except for three comparisons with anakinra.

A 2008 meta-analysis of 12 randomized, controlled clinical trials suggested a clear benefit of anti-TNF agents over placebo or methotrexate in the treatment of rheumatoid arthritis (RA). Patients with late disease appeared to have higher response, irrespective of the anti-TNF agent used, than patients with intermediate to early disease. Although there were no head-to head trials,

the authors concluded that infliximab, etanercept, and adalimumab have similar overall efficacy in RA.

In March 2007, the Canadian Agency for Drugs and Technologies in Health issued an HTA Technology Report, "Infliximab and Etanercept in Rheumatoid Arthritis; Systematic Review of Long-term Clinical Effectiveness, Safety, and Cost-Effectiveness." The authors concluded infliximab and etanercept used concomitantly with methotrexate have moderate efficacy in the long-term treatment of active RA that is resistant to conventional therapy. The short-term (less than 12 months) safety profile was found acceptable. The long-term safety remains a concern. The economic review shows that costs per quality-adjusted life year (QALY) are high (greater than $100,000 for a QALY), surpassing the generally accepted thresholds for cost-effectiveness. The results suggest that infliximab with methotrexate, and etanercept with methotrexate are only cost-effective as second-line therapies after failure with traditional disease-modifying anti-rheumatic drugs (DMARDs).

Several studies have addressed dose escalation of infliximab for RA. Two studies found better treatment response after increasing infliximab dosage up to 10 mg/kg. Adverse events were not significantly different in one study. However, Pavelka and colleagues found treatment efficacy did not improve and toxicity increased moderately after increasing infliximab dosage to 5 mg/kg.

In 2012, van Vollenhoven and colleagues reported on the two-year results of the randomized, non-blinded Swefot trial (Swedish Pharmacotherapy), which compared conventional combination treatment for RA to treatment with infliximab in 258 patients refractory to methotrexate. Treatment response was not significantly different clinically between groups at 18 and 24 months and radiographically between groups at 18 months. However, the treatment group that received infliximab had less radiologic disease progression at 24 months (4·00 [standard deviation, SD: 10·0] vs. mean 7·23 [12·72]; p=0·009).

Sarcoidosis

Sarcoidosis is a systemic granulomatous disease of unknown cause affecting young and middle-aged adults. Doty et al reported on the treatment of sarcoidosis with infliximab. The indications for treatment of sarcoidosis are not standardized. Systemic corticosteroids are first-line therapy for patients who require therapy. Some patients are unable to tolerate the side effects of corticosteroids or are refractory to this therapy. Other alternative agents available are cytotoxic and noncytotoxic. Evidence is demonstrating the effectiveness of tumor necrosis factor (TNF)-α in the pathogenesis of granulomatous inflammation, and reports of successful treatment of sarcoidosis with agents having anti-TNF activity have been published.

An analysis from a previously published randomized trial of 138 patients with pulmonary sarcoidosis was published. The observed treatment benefit in extrapulmonary sarcoidosis patients receiving infliximab for 24 weeks was reported as an improvement in extrapulmonary Physician Organ Severity Tool, a metric designed for the present study that summarizes the involvement of 17 organs. While a statistical improvement in group-mean score was noted at 24 weeks, this measure has not been clinically validated, and its relationship to clinical outcomes is unknown. The accompanying editorial concluded that "a routine role for infliximab has not been established by these data." In a subsequent publication from the same authors, levels of

inflammatory serum proteins were reduced in 134 sarcoidosis patients compared to 50 controls. The authors noted the need for further studies. Maneiro and colleagues conducted a systematic review of sarcoidosis treatment with TNF blockers. The authors found insufficient evidence to support the use of TNF blockers in the treatment of sarcoidosis.

Scleroderma (Systemic Sclerosis)
A 2011 systematic review evaluated three studies on biologic agents for systemic sclerosis. Infliximab and etanercept treatment resulted in improved inflammatory arthritis and disability scores on the Health Assessment Questionnaire Disability Index. The reviewers noted the need for larger, long-term studies to understand the role of biologics in treatment of scleroderma.

Sjögren Syndrome
A 2010 systematic review found anti-tumor necrosis factor agents have not demonstrated effectiveness in the treatment of Sjogren syndrome. Included in the review were two placebo-controlled studies of infliximab and etanercept and two trials of fewer than 30 patients. The placebo-controlled studies did not improve joint pain, fatigue, or dryness, as measured by a composite visual analog scale, and the authors concluded these agents were not clinically effective.

Takayasu's arteritis
Takayasu's arteritis is a granulomatous inflammatory disease affecting large arteries and occurring primarily in children and young women. The incidence in the United States is estimated at 2.6 cases per million persons per year.

The disease affects all sections of the aorta and the major arteries leading from the aorta. When the aorta itself is involved, the lesions are usually patchy, with normal vessel between lesions, although involvement of the entire aorta is sometimes seen. Because of the critical nature of the vessels involved, patients may present with strokes, claudication of the upper extremities, myocardial infarction, hypertension due to renal artery stenosis, or mesenteric ischemia. In addition to the aorta, the disease may affect the aortic valve and pulmonary vessels.

The clinical presentation is a combination of symptoms related to the particular vessels involved, plus a variety of nonspecific systemic symptoms. The patient may complain of upper extremity claudication, hypertension, pain over the carotid arteries, dizziness, visual abnormalities, chest wall pain, pain in various joints, malaise, fever, weight loss, and night sweats. Although joint pain may be severe, actual synovitis is mild and is seen in only approximately half the patients complaining of joint pain. As the disease progresses, cardiac symptoms often become prominent, with aortic insufficiency and coronary artery disease both taking their toll. Congestive heart failure and massive hemoptysis from pulmonary artery involvement may occur at any time in the course of the disease.

Because the disease is rare, there are very few published studies looking at the use of anti-TNF agents in the treatment of Takayasu's arteritis. Dr. Peter Merkel and colleagues at Boston University School of Medicine have hypothesized that because granulomatous inflammation is a typical feature of Takayasu's arteritis and TNF is an important factor for granuloma formation,

anti-TNF agents may be useful in the management of the disease. In their study of 15 relapsing and mostly treatment-resistant patients, they found that 87% of patients achieved a period-sustained remission while on Remicade and off corticosteroids therapy. Twenty-seven percent (27%) of patients achieved a partial remission and had lower corticosteroid requirements.

Ulcerative Colitis

Studies for the use of Remicade for the treatment of ulcerative colitis (UC) have included small numbers of patients and short-term follow-up. There is also a lack of consistency in dosage and response. Chey et al published in 2001 the results of a study that included eight patients with ulcerative colitis that was refractory to usual combination medical therapy. This study included patients that were at a last resort before surgical intervention. Each received 5mg/kg single infusion, with no relapses at time of reporting. Follow-up was reported at two to four months. The conclusion stated that it would be appropriate to undertake randomized clinical trials for patients with active ulcerative colitis.

Chey et al again reported on a study in 2001 of 16 patients with severe, corticosteroid refractory ulcerative colitis. Remission occurred in 14 or 16 patients greater than or equal to four months and in four of 16 for seven to ten months follow-up. Six of 16 received a second infusion after five months. Several were completely withdrawn from steroid therapy. Dosage ranged from 5mg/kg to 20mg/kg, no correlation was mentioned between dosage and response in this study.

Sands et al reported in 2001 on a study of 11 patients. The study was originally designed for 60 patients but due to slow enrollment the study was terminated prematurely. This was a double-blind, placebo controlled study. Patients enrolled had severe, active steroid refractory ulcerative colitis. Dosages remained from 5mg/kg to 20mg/kg. Endpoint was defined as treatment failure after two weeks post-infusion. Eight of 11 patients were successes after two weeks. The remaining three were not successes after placebo. Only two patients received 20 mg/kg and neither underwent either elective or non-elective colectomy. Regardless of the low numbers for participation, Remicade was well tolerated and may provide clinical benefit to patients with severe, steroid-refractory UC.

In 2002, Su et al reported on a study of 27 patients with active UC. Dosage of infliximab was 3 to 5mg/kg. Of the 27 patients, 12 patients achieved remission, six patients had partial response, nine patients had no response and five later had colectomy. Nine of the 18 with a response had 19 relapses. Eight of those nine responded to repeat treatment. Median follow-up was four months. Fourteen had a single infusion, 13 had more than one over median of 13 months. Most common interval was between six to eight weeks. In this study the authors noted that patients with steroid-refractory disease were less likely to respond to infliximab than were steroid-responsive patients (33%-83%). The conclusion also suggested that in infliximab was effective in treating medically refractory severe ulcerative colitis.

The 2005 approval by the U.S. Food and Drug Administration (FDA) of infliximab for the treatment of ulcerative colitis was based in part on the results of ACT 1 and ACT 2 randomized studies. These studies enrolled patients with disease refractory to at least one standard therapy, including corticosteroids, immunosuppressants, or mesalamine. Patients received infliximab or placebo infusions at 0, 2, and 6 weeks and then every eight weeks thereafter. The ACT 1 trial

continued infusions until week 46, with final evaluation at week 54. In contrast, the ACT 2 trial continued infusions until week 22, with final evaluation at week 30. The primary endpoint of both trials was induction of clinical response, while secondary endpoints included clinical remission. In both studies, the infliximab group had a significant improvement in both clinical response and clinical remission at all-time points studied. Also, a significantly greater percentage of patients in the infliximab group were able to discontinue steroids while in clinical remission. Based on the results of these studies, the FDA gave infliximab priority review.

Additional, reviews of infliximab for the treatment of ulcerative colitis were published in 2009 and 2010. The reviews found infliximab treatment is appropriate for acute exacerbations of severely active ulcerative colitis when cyclosporine is not appropriate or contraindicated.

In 2012, Reinisch and colleagues reported on the long-term extension trial on 229 patients from the ACT-1 and ACT-2 trials. The safety profile during the extension trial was consistent with the original trials, and infliximab continued to be effective for up to three years. However, infliximab was discontinued in 70 (30.6%) patients due to adverse events, lack of efficacy, and other reasons.

In 2013, Chang and colleagues performed a meta-analysis to evaluate the outcomes of UC patients receiving infliximab or cyclosporine as rescue therapy in acute severe steroid-refractory exacerbations. Six retrospective cohort studies (published through May 2012) describing 321 patients met the inclusion criteria. The meta-analysis did not show significant differences between infliximab and cyclosporine in the 3-month colectomy rate (odds ratio (OR), 0.86; 95% CI, 0.31–2.41, p = 0.775), in the 12-month colectomy rate (OR, 0.60; 95% CI, 0.19–1.89, p = 0.381), in adverse drug reactions (OR, 0.76; 95% CI, 0.34–1.70; p = 0.508), and in postoperative complications (OR, 1.66; 95% CI, 0.26–10.50; p = 0.591). Several limitations need to be acknowledged in this meta-analysis, including study populations being uncontrolled and potentially heterogeneous, discrepancies in the dosage and serum levels of cyclosporine used across studies, and the accrual period of these studies ranged from 1993 to 2011, a period that has seen major advancement in the use of laparoscopic surgical techniques and devices which may a major impact on the overall management of these patients and contributed to their operative outcomes.

In 2012, Yang and colleagues performed a meta-analysis of observational studies (published through August 2012) to determine the relationship between preoperative infliximab use and early postoperative complications in UC patients undergoing abdominal surgery. A total of 13 studies involving 2,933 patients were included in this meta-analysis. There was no significant association between infliximab therapy preoperatively and total (OR, 1.09; 95% CI, 0.87–1.37, p = 0.47), infectious (OR, 1.10; 95% CI, 0.51–2.38, p = 0.81) and non-infectious (OR, 1.10; 95% CI, 0.76–1.59, p = 0.61) postoperative complications respectively. A significantly decreased risk for infectious complications was reported with infliximab use within 12 weeks prior to surgery (OR, 0.43; 95% CI, 0.22–0.83, p = 0.01). No publication bias was observed across studies. Significant heterogeneity however was observed when combining these studies with regard to the infectious complications.

Several prospective trials have been published regarding the use of Remicade for pediatric patients with ulcerative colitis.

Hyams et al conducted a randomized multicenter, open-label Phase II study to evaluate the efficacy and safety of Remicade in pediatric patients with moderate to severe UC. Base line demographics and disease characteristics were comparable among the 60 patients in the study. Clinical response was achieved in 73.3% (n=44/60) patients and clinical remission was achieved in 40% of the patients. Remicade was well tolerated with no deaths, malignancies, or opportunistic infections.

Hyams et al also conducted a prospective, multicenter cohort study in 332 patients with UC. Remicade was administered to 16% (n=52) of the patients. Most of the patients were more likely to have had corticosteroids or immunomodulation by three months after diagnosis. At 3, 6, 12, and 24 months the likelihood of continuing Remicade therapy was 76%, 66%, 59%, and 44%.

Turner et al performed a prospective multicenter study on Remicade as a salvage therapy in children. Of 128 children, 37 patients did not respond and needed salvage therapy. Remicade was administered to 33 of the patients with 25 responding. Of the eight responders, all had new onset disease, more active disease and shorter disease duration.

In a 2011 systematic review of pediatric ulcerative colitis treatment, data from six studies on infliximab, consisting of 126 pediatric patients, yielded a short-term pooled response of 75% (95% CI: 67-83%) with a one-year pooled response of 64% (95% CI: 56-72%). The FDA approval of infliximab for pediatric use in 2011 was based on data from a Phase 3 randomized, multicenter, open-label study of moderately to severely active ulcerative colitis patients aged 6-17 years. Patients in the study were refractory or unable to tolerate standard therapy with 6-mercaptopurine, azathioprine, corticosteroids, or 5-aminosalicylate. In this study, 73% (44/60) of patients responded to infliximab at eight weeks. Adverse events were similar to infliximab use in adult populations. In a 2010 prospective multi-center study, children with severe ulcerative colitis were treated with infliximab after failed intravenous corticosteroids. Twenty-five out of 33 patients responded to infliximab, which was considered to be effective.

Uveitis

Four small studies (n=10 to 13 treated with infliximab) of both multiple etiology uveitis and Behcet's uveitis were published. No control groups were included in these studies, which ranged in follow-up duration from 12 to 36 months. Visual acuity, inflammation, and episodes of recurrent severe uveitis were the outcomes of interest. For the two prospective open-label trials, three of 10 (30%) patients were free of recurrence at 24 months, and seven of 12 (58%) patients were free of recurrence at 36 months. These small studies are promising; yet without control groups, they do not provide enough to determine impact on clinical outcomes.

In 2013, Cordero-Coma and colleagues published a systematic review regarding the use of anti-TNF agents for managing uveitis patients. A total of 54 studies (published through October 2011) were included in this review. The evidence base for infliximab consisted of four open trials, one cross-sectional study, 12 prospective studies, and 33 retrospective studies and/or case series. A total of 517 patients who met all inclusion criteria were included in this systematic

review. Based on the review of the evidence, the investigators rated the level of evidence for infliximab for the treatment of noninfectious immune-mediated uveitis as level 2b (findings based on extrapolation from individual cohort study, or low-quality randomized controlled trials). This review, however, has several limitations, including poor study design, heterogeneity of the study variables, lack of standardized methods to assess treatment efficacy for uveitis and variable treatment outcome measures.

Wegener's Granulomatosis (WG)

Wegener's Granulomatosis (WG) is a rare disorder of possible autoimmune origin and is classified as one of the rheumatic diseases that cause vasculitis in the upper respiratory tract, lungs and kidneys. Wegener's Granulomatosis occurs most often between the ages of 30 and 50 and more in men than women.

Many other areas of the body may also be affected, with arthritis occurring in almost half of all cases. The eyes and skin may also be affected. Destructive lesions develop in the upper and lower respiratory tract and the kidney. The kidney lesions cause glomerulonephritis that may result in hematuria and kidney failure.

Symptoms may include fatigue, malaise, fever and a sense of discomfort around the nose and sinuses. Upper respiratory infections such as sinusitis or ear infections frequently precede the diagnosis of Wegener's Granulomatosis. Loss of appetite and weight loss are common as well as skin lesions.

Treatment aims are to limit the extent and severity of permanent organ damage by controlling the disease promptly and to minimize the short-and long-term morbidity that often results from therapy. Corticosteroids are the cornerstone of treatment. Cyclophosphamide may be added. Methotrexate may also be used with the corticosteroids to assist in inducing remission. Other drugs that may be used are azathioprine, trimethoprim-sulfamethoxazole, and intravenous immunoglobulin (IVIG) may be used in refractory cases. Trials are also underway evaluating anti-tumor necrosis factor and other biologic approaches to treatment. These drugs include etanercept and infliximab.

Lamprecht et al reported on the effectiveness of infliximab in combination with cyclophosphamide in refractory, biopsy proven Wegener's Granulomatosis. Six patients with refractory WG were evaluated after receiving infliximab. Remission was induced in five patients and remained in remission for six to 24 months of follow-up. Bartolucci et al reported on 10 patients with refractory systemic vasculitis, seven of these patients had WG. Complete or partial remission was observed in all patients. After 42 days, corticosteroid dose was reduced, discontinued or remained stable and all were initiated or continued on immunosuppressant therapy. The authors concluded that Remicade induced prompt symptomatic response in patients with systemic vasculitis not responding to conventional treatment.

Other Uses

In addition to its labeled uses, infliximab is being studied in treatment-refractory inflammatory diseases and other varied indications. The discussion here will include only publications reporting the use of infliximab or other TNF-alpha blocking agents in 10 or more patients.

Two systematic reviews were published in 2013 to evaluate the evidence-base for the use of anti-TNF agents in hidradenitis suppurativa; based on data from observational studies, moderate to good response rates were observed in over 80% of the patients treated with infliximab. However, the quality of evidence was overall of low quality and differed between the agents, making direct comparisons difficult.

Studies, which should be viewed as preliminary, are being reported on use of infliximab for treatment of refractory Kawasaki syndrome, sacroiliitis, severe alcoholic hepatitis, systemic lupus erythematosus, and diabetic macular edema. In addition, a publication reported on positive results from intra-articular injections of infliximab for treatment of refractory inflammatory monoarthritis in patients with ankylosing spondylitis.

Other publications suggested potentially useful indications. One is a case series of refractory systemic necrotizing vasculitides, where, over 35 months of follow-up, 11 of 15 patients entered remission and five of 15 patients achieved sustained remission (>6 months). However, ten patients relapsed after a median of 13 months. One report of two Phase II trials of infliximab as a treatment for refractory renal cell carcinoma (n=18 treated with 10 mg/kg, n=19 treated with 5mg/kg) showed partial response or stable disease, with 61% of those receiving the higher dose showing stable disease with a median duration of 7.7 months. One death due to infection was reported as well.

A number of placebo-controlled trials of infliximab were conducted for other indications such as polymyalgia rheumatica (n=51), giant cell arteritis (n=44), endometriosis (n=21), sclerosing cholangitis (n=24), pancreatic cancer cachexia (n=89), non-small cell lung cancer-related weight loss (n=61), depression, and graft-versus-host disease. None of these trials showed a clinical benefit of infliximab in their stated outcomes. While small sample sizes may account for some lack of reported effect due to study power, two studies [giant cell arteritis, sclerosing cholangitis] were terminated early due to lack of treatment effect at interim analysis. Other studies reported negative results as well. Infliximab was not effective in the treatment of age-related macular degeneration in an unmasked, pilot, randomized, single-center Phase I/II study. Intra-articular injections of infliximab were not effective in treating chronic or recurrent gonarthritis in a randomly assigned, crossover study of 23 patients (41 total intra-articular injections: 20 infliximab and 21 methylprednisolone). In this study, improvements were greater with methylprednisolone. Additionally, infliximab did not improve clinical outcomes in a prospective longitudinal study of 44 patients with giant-cell arteritis.

The placebo-controlled studies reporting minimal or no benefit of infliximab treatment in a variety of inflammatory diseases where epidemiologic evidence had suggested benefits are especially sobering, given the drug's toxicities. Well-designed, comparative studies are imperative.

Summary

Infliximab (Remicade® Centocor) is a tumor necrosis factor (TNF) alpha 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 administered via intravenous infusion.

In summary, head-to-head comparative trials that have evaluated the relative efficacy of the TNF-blocking agents in the treatment of the various conditions are limited. However, the literature which includes several systematic reviews does consider the TNF-blocking agents primarily infliximab, adalimumab, and etanercept to have similar efficacy in rheumatoid arthritis, ankylosing spondylitis**,** psoriatic arthritis, and plaque psoriasis. For the maintenance of Crohn's disease remission, the TNF-blocking agents, infliximab, adalimumab, and certolizumab are considered to have clinical efficacy. Infliximab has the additional approved indication for fistula healing. Adalimumab and etanercept are both administered subcutaneously, which may be more advantageous to the intravenous administration of infliximab.

Given the lack of comparative trials and randomized controlled trials for agents across conditions, the evidence does not definitively demonstrate that clinical outcomes are equivalent for the various TNF-blocking agents. The policy statements that infliximab may be considered medically necessary remain unchanged.

The use of infliximab is considered investigational in all other indications, as listed in the policy statements, as the available evidence is preliminary or not in support of the use of infliximab for these conditions.

Practice Guidelines and Position Statements

The American College of Rheumatology's (ACR) 2011 Model Biologics Policy indicates infliximab may be used off-label for the following indications: undifferentiated polyarthritis, undifferentiated spondyloarthropathy, sarcoidosis, myositis, Behcet's disease, uveitis, adult-onset Still's disease, reactive arthritis, juvenile idiopathic arthritis, and autoinflammatory diseases. The ACR also recommends dose escalation of infliximab to 10 mg/kg in patients with rheumatoid arthritis or Crohn's disease that does not completely respond to induction dosage.

In 2011, the World Congress of Gastroenterology issued the London Position Statement on biologics for inflammatory bowel disease. Infliximab is considered appropriate for the treatment of Crohn's disease after surgical drainage of any sepsis when the disease is steroid-refractory, steroid-dependent, or complex fistulizing. Infliximab is also considered appropriate for moderate or severe, refractory ulcerative colitis. The position statement also indicates TNF blocker dose adjustments may be appropriate when there is decrease or loss of response to treatment with biologics. Data on when TNF blocker treatment can be discontinued is noted to be insufficient.

A 2010 task force of the National Psoriasis Foundation developed consensus treatment recommendations for erythrodermic or exfoliative psoriasis. These recommendations indicate infliximab and cyclosporine are first-line agents that act rapidly for treatment of this indication. However, the availability of data on the treatment of erythrodermic psoriasis is limited, and the need for further studies is noted.

In March 2006, the American Gastroenterological Association Institute released a medical position statement on corticosteroids, immunomodulators, and infliximab in inflammatory bowel

disease on behalf of the American Gastroenterological Association (AGA). These recommendations are intended for adult patients and are based on the interpretation and assimilation of scientifically valid research. The ideal was to provide evidence based on prospective, randomized placebo-controlled trials; however, when this was not possible, the use of experts' consensus was used. The recommendation for infliximab is for the treatment of patients with inflammatory and fistulizing Crohn's disease (CD) that failed to respond to other therapies. In October 2006, the FDA approved expanding the indications for infliximab to include reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.

In May 2008, the American Academy of Dermatology released guidelines for the management of psoriasis and psoriatic arthritis. These guidelines address the treatment of both adult and childhood psoriasis and psoriatic arthritis including biologics.

Orencia (abatacept)
Per the package labeling, Abatacept inhibits T-cell activation by binding to CD80 and CD86. This interaction provides a co-stimulatory signal necessary for full activation of T-lymphocytes, implicated in the pathogenesis of rheumatoid arthritis.

The efficacy and safety of abatacept were assessed in five randomized, double blind, and placebo-controlled studies in patients 18 and older with active RA diagnosed according to American College of Rheumatology (ACR) criteria. These trials included more than 2,600 patients. The Phase III trial program included three major double-blind randomized placebo controlled studies: AIM (Abatacept in Inadequate responders to Methotrexate), which compared Orencia in combination with MTX to MTX alone: ATTAIN (Abatacept Trial in Treatment of Anti-TNF Inadequate responders), which compared Orencia in combination with non-biologic DMARDs to non-biologic DMARDs alone in patients with an inadequate efficacy response to the TNF antagonists etanercept and infliximab; and ASSURE (Abatacept Study of Safety in Use with other RA therapies), which studied the safety of Orencia compared to placebo when used in combination with a variety of biologic and non-biologic DMARDs.

In both AIM and ATTAIN, Orencia demonstrated significant and sustained improvement of the signs and symptoms of RA as measured by American College of Rheumatology (ACR) 20, 50, and 70 scores, with significant difference from placebo by day 15 for ACR 20 in some patients, which was the first follow-up visit after the first dose. In both trials, significant improvements in physical function were noted as compared to placebo. ACR responses and improvements in physical function were maintained up to three years in Phase II trial of patients with inadequate response to MTX.

A significant proportion of patients taking Orencia plus MTX achieved a major clinical response, defined as maintaining an ACR score for six consecutive months, compared to those treated with MTX alone in AIM. In AIM, structural damage was slowed in patients treated with Orencia plus MTX, compared to those treated with MRX alone.

Concurrent therapy with Orencia and a biologic DMARD is not recommended. Patients receiving concomitant Orencia and TNF antagonist therapy experienced more infections and serious infections compared to patients treated with only TNF antagonists, without an important enhancement of efficacy. Treatment with Orencia should be discontinued if a patient develops a serious infection. Patients should be screened for tuberculosis and if positive, should be treated with standard medical practice prior to therapy with Orencia.

Orencia is currently being investigated in the following disease areas in Phase II/III clinical trials: systemic lupus erythematosus (SLE), early rheumatoid arthritis, and juvenile rheumatoid arthritis.

The safety and efficacy of Remicade were assessed in a randomized, open-label study in 112 pediatric patients six 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-mercaptopurine, azathioprine, or methotrexate; 35% were also receiving corticosteroids at baseline. All patients received induction dosing of 5mg/kg Remicade at weeks 0, 2, and 6. The proportion of pediatric patients achieving clinical response at week 10 compared favorably with the proportion of adults achieving a clinical response. At both week 30 and week 54, the proportion of patients in clinical response was greater as well as those in clinical remission in the every eight week treatment group than in the every 12 week treatment group. The proportion of patients able to discontinue corticosteroids while in remission at week 30 was 46% for the every eight week maintenance group and 33% for the every 12 week maintenance group. By week 54, the proportion of patients able to discontinue corticosteroids while in remission was 46% for the every eight week maintenance group and 17% for the every 12 week maintenance group.

Adverse events for 103 randomized pediatric patients had some differences when compared to the adults with Crohn's patients. These included anemia, blood in stool, leukopenia, flushing, viral infection, neutropenia, bone fracture, bacterial infection and respiratory tract allergic reaction. In the post marketing, experience with Remicade in the pediatric population has included malignancies, transient hepatic enzyme abnormalities, lupus-like syndromes and the development of autoantibodies.

The safety and efficacy of Remicade were assessed in three randomized, double-blind, placebo-controlled studies in patients 18 years of age and older with chronic, stable plaque psoriasis involving ≥ 10% body surface area (BSA), a minimum Psoriasis Area and Severity Index (PASI) 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. Results of the EXPRESS study showed that eight out of 10 patients on Remicade achieved PASI 75 at week 10, and eight out of 10 patients sustained PASI 75 through week 24. These results were confirmed in the EXPRESS II and SPIRIT studies.

Juvenile idiopathic arthritis (JIA) is the term used to describe arthritis-inflammation of the synovium with an onset prior to the age of 16. Previously called juvenile rheumatoid arthritis, the name has been changed to reflect the difference between the juvenile and adult forms of arthritis. There are five main types of JIA based on the number of joints involve during the first six months of disease and the involvement of other organs. The types of JIA are oligoarthritis, (involves less than five joints); polyarthritis, (involves more than five joints); systemic arthritis (high fevers, rash and inflammation of other organs); enthesitis-related arthritis, (spine, hips and entheses which is the attachment points of tendons to bones and is mainly seen in males over eight years of age); and psoriatic arthritis (arthritis with rash of psoriasis).

The safety and efficacy of abatacept were assessed in a three-part study including an open-label extension in children with polyarticular juvenile idiopathic arthritis (JIA). One-hundred ninety patients ages 6 to 17 years of age with moderately to severely active polyarticular JIA with an inadequate response to one or more DMARDS, such as MTX or TNF antagonists were included in the study. Patients for inclusion was a disease duration of approximately four years, based on baseline counts of active joints, joints with loss of motion, elevated C-reactive protein levels and ESR. Patients also had subtypes of JIA. At the beginning of the study 74% were receiving MTX and remained on a stable dose of MTX (those not currently taking MTX did not start on MTX during this study).

In the first phase of the study, patients received 10mg/kg intravenously at day 1, 15, 29 and monthly thereafter. Responses were graded according to the American College of Radiology's Pediatric 30 definition of improvement, (≥ 30% improvement in at least three of the six JIA core set variables and ≥ 30% worsening in not more than one of the six JIA core set variables). Patients who demonstrated an ACR Pedi 30 response at the end of the initial study were randomized into the double-blind phase to receive either abatacept or placebo for six months or until disease flare. During the second phase, the abatacept group had significantly fewer disease flares compared to placebo patients (20% vs 53%) with a 95% CI. The risk for disease flare among patients that continued on abatacept was less than one third that for the patients that were withdrawn from abatacept treatment. (Prescribing information for Orencia 4/2008)

Cimzia (certolizumab pegol)
The following information was taken from the Prescribing Information for Cimzia (certolizumab pegol).

Crohn's Disease
Cimzia is a tumor necrosis factor (TNF) blocker. Cimzia was shown to neutralize membrane-associated and soluble human TNF α in a dose-dependent manner. The efficacy and safety of Cimzia were assessed in two double-blind, randomized, placebo-controlled studies in patients aged 18 years and older with moderately to severely active Crohn's disease, as defined by a Crohn's disease. Cimzia was administered subcutaneously at a dose of 400mg in both studies. Stable concomitant medications for Crohn's disease were permitted. The results of Study CD1 demonstrated week six; the proportion of clinical responders was statistically significantly greater for Cimzia-treated patients compared to controls. The difference in clinical remission rates was not statistically significant at week six. The difference in the proportion of patients who were in clinical response at both weeks six and 26 was also statistically significant,

demonstrating maintenance of clinical response. Study CD2 was a randomized treatment-withdrawal study in patients with active Crohn's disease. The results for clinical response and remission demonstrated at week 26, a statistically significantly greater proportion of week six responders were in clinical response and in clinical remission in the Cimzia treated group compared to the group treated with placebo.

Rheumatoid Arthritis

The safety and efficacy of Cimzia were assessed in four randomized, placebo-controlled, double-blind studies in patients ≥ 18 years of age with moderately to severely active rheumatoid arthritis diagnosed according to the American College of Rheumatology (ACR) criteria. Patients had ≥nine swollen and tender joints and had active RA for at least six months prior to baseline. Cimzia was administered subcutaneously in combination with MTX at stable doses of at least 10 mg weekly in Studies RA-I, RA-II, and RA-III. Cimzia was administered as monotherapy in Study RA-IV.

Study RA-I and Study RA-II evaluated patients who had received MTX for at least six months prior to study medication, but had an incomplete response to MTX alone. Patients were treated with a loading dose of 400mg at weeks 0, 2 and 4 (for both treatment arms) or placebo followed by either 200mg or 400mg of Cimzia or placebo every other week, in combination with MTX for 52 weeks in Study RA-I and for 24 weeks in Study RA-II. Patients were evaluated for signs and symptoms and structural damage using the ACR20 response at week 24 (RA-I and RA-II) and modified Total Sharp Score (mTSS) at week 52 (RA-I). The open-label extension follow-up study enrolled 846 patients who received 400mg of Cimzia every other week.

Study RA-III evaluated 247 patients who had active disease despite receiving MTX for at least six months prior to study enrollment. Patients received 400mg of Cimzia every four weeks for 24 weeks without a prior loading dose. Patients were evaluated for signs and symptoms of RA using the ACR20 at week 24.

Study RA-IV (monotherapy) evaluated 220 patients who had failed at least one DMARD use prior to receiving Cimzia. Patients were treated with Cimzia 400mg or placebo every four weeks for 24 weeks. Patients were evaluated for signs and symptoms of active RA using the ACR20 at week 24.

The percent of Cimzia-treated patients achieving ACR20, 50 and 70 responses in Studies RA-I and RA-IV are available. Cimzia-treated patients had higher ACR20, 50, and 70 response rates at six months compared to placebo-treated patients. The results in study RA-III (247 patients) were similar to a those seen in study RA-IV. Over the one-year Study RA-I, 13% of Cimzia-treated patients achieved a major clinical response, defined as achieving and ACR70 response over a continuous six-month period, compared to 1% of placebo-treated patients.

In studies RA-I, RA-II, RA-III, and RA-IV, Cimzia-treated patients achieved greater improvement from baseline than placebo-treated patients in physical function as assessed by the Health Assessment Questionnaire-Disability Index (HAD-DI) at week 24 (RA-II, RA-III and RA-IV) and at week 52 (RA-I).

Psoriatic Arthritis

The efficacy and safety of CIMZIA were assessed in a multi-center, randomized, double-blind, placebo controlled trial (PsA001) in 409 patients aged 18 years and older with active psoriatic arthritis despite DMARD therapy. Patients in this study had ≥ 3 swollen and tender joints and adult-onset PsA of at least 6 months' duration as defined by the Classification Criteria for Psoriatic Arthritis (CASPAR) criteria, and increased acute phase reactants. Patients had failed one or more DMARDs. Previous treatment with one anti-TNF biologic therapy was allowed, and 20% of patients had prior anti-TNF biologic exposure. Patients receiving concomitant NSAIDs and conventional DMARDs were 73% and 70 % respectively.

Patients received a loading dose of CIMZIA 400 mg at weeks 0, 2 and 4 (for both treatment arms) or placebo followed by either CIMZIA 200 mg every other week or CIMZIA 400 mg every 4 weeks or placebo every other week. Patients were evaluated for signs and symptoms and structural damage using the ACR20 response at week 12 and modified Total Sharp Score (mTSS) at Week 24.

Clinical Response

The percentage of CIMZIA-treated patients achieving ACR20, 50 and 70 responses in study PsA001 are shown in Table 1. ACR20 response rates at weeks 12 and 24 were higher for each CIMZIA dose group relative to placebo (95% confidence intervals for CIMIZIA 200 mg minus placebo at weeks 12 and 24 of (23%, 45%) and (30%, 51%), respectively and 95% confidence intervals for CIMZIA 400 mg minus placebo at weeks 12 and 24 of (17%, 39%) and (22%, 44%), respectively).

Patients with enthesitis at baseline were evaluated for mean improvement in Leeds Enthesitis Index (LEI). CIMZIA-treated patients receiving either 200 mg every two weeks or 400 mg every four weeks showed a reduction in enthesitis of 1.8 and 1.7, respectively as compared with a reduction in placebo-treated patients of 0.9 at week 12. Similar results were observed for this endpoint at week 24. Treatment with CIMZIA resulted in improvement in skin manifestations in patients with PsA. However, the safety and efficacy of CIMZIA in the treatment of patients with plaque psoriasis has not been established.

Table 1: ACR Responses in Study PsA001 (Percent of Patients)

Response[c]	**Placebo** **N=136**	**CIMZIA[a] 200 mg Q2W** **N=138**	**CIMZIA[b] 400 mg Q4W** **N=135**
ACR20			
Week 12	24%	58%	52%
Week 24	24%	64%	56%
ACR50			
Week 12	11%	36%	33%
Week 24	13%	44%	40%
ACR70			
Week 12	3%	25%	13%
Week 24	4%	28%	24%

(a) CIMZIA administered every 2 weeks preceded by a loading dose of 400 mg at weeks 0, 2 and 4

(b) CIMZIA administered every 4 weeks preceded by a loading dose of 400 mg at weeks 0, 2 and 4
(c) Results are from the randomized set. Non-responder Imputation (NRI) is used for patients who escaped therapy or had missing data.

Radiographic Response
In study PsA001, inhibition of progression of structural damage was assessed radiographically and expressed as the change in modified total Sharp score (mTSS) and its components, the Erosion Score (ES) and Joint Space Narrowing score (JSN) at week 24, compared to baseline. The mTSS score was modified for psoriatic arthritis by addition of hand distal interphalangeal (DIP) joints.

Patients treated with CIMZIA 200 mg every other week demonstrated greater reduction in radiographic progression compared with placebo-treated patients at Week 24 as measured by change from baseline in total modified mTSS Score (estimated mean score was 0.18 in the placebo group compared with -0.02 in the CIMZIA 200 mg group; 95% CI for the difference was (-0.38, -0.04)). Patients treated with CIMZIA 400 mg every four weeks did not demonstrate greater inhibition of radio graphic progression compared with placebo-treated patients at Week 24.

Physical Function Response
In Study PsA001, CIMZIA-treated patients showed improvement in physical function as assessed by the Health Assessment Questionnaire – Disability Index (HAQ-DI) at week 24 as compared to placebo (estimated mean change from baseline was 0.19 in the placebo group compared with 0.54 in the CIMZIA 200 mg group; 95% CI for the difference was (-0.47, -0.22) and 0.46 in the CIMZIA 400 mg group; 95% CI for the difference was (-0.39, -0.14)).

Ankylosing spondylitis
The efficacy and safety of CIMZIA were assessed in one multicenter, randomized, double-blind, placebo-controlled study (AS-1) in 325 patients ≥18 years of age with adult-onset active axial spondyloarthritis for at least 3 months. The majority of patients in the study had active AS.

Patients had active disease as defined by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥4, and spinal pain ≥4 on a 0 to 10 Numerical Rating Scale (NRS). Patients must have been intolerant to or had an inadequate response to at least one NSAID. Patients were treated with a loading dose of CIMZIA 400 mg at weeks 0, 2 and 4 (for both treatment arms) or placebo followed by either 200 mg of CIMZIA every two weeks or 400 mg of CIMZIA every four weeks or placebo. Concomitant NSAIDs were received by 91% of the AS patients. The primary efficacy variable was the proportion of patients achieving an ASAS20 response at week 12.

Clinical Response
In study AS-1, at week 12, a greater proportion of AS patients treated with CIMZIA 200mg every two weeks or 400mg every four weeks achieved ASAS 20 response compared to AS patients treated with placebo. Responses were similar in patients receiving CIMZIA 200 mg every two weeks and CIMZIA 400 mg every four weeks.

Stelara (ustekinumab)
The following information was taken from the Prescribing Information for Stelara (ustekinumab).

Plaque psoriasis (Ps)
Two multicenter, randomized, double-blind, placebo-controlled studies (STUDY 1 and STUDY 2) enrolled a total of 1996 subjects 18 years of age and older with plaque psoriasis who had a minimum body surface area involvement of 10%, and Psoriasis Area and Severity Index (PASI) score ≥ 12, and who were candidates for phototherapy or systemic therapy. Subjects with guttate, erythrodermic, or pustular psoriasis were excluded from the studies.

STUDY 1 enrolled 766 subjects and STUDY 2 enrolled 1230 subjects. The studies had the same design through week 28. In both studies, subjects were randomized in equal proportion to placebo, 45 mg or 90 mg of Stelara. Subjects randomized to Stelara received 45 mg or 90 mg doses, regardless of weight, at weeks 0, 4 and 16. Subjects randomized to receive placebo at weeks 0 and 4 crossed over to receive Stelara (either 45 mg or 90 mg) at weeks 12 and 16.

In both studies, the endpoints were the proportion of subjects who achieved at least a 75% reduction in PASI score (PASI 75) from baseline to week 12 and treatment success (cleared or minimal) on the Physician's Global Assessment (PGA). The PGA is a six-category scale ranging from 0 (cleared) to 5 (severe) that indicates the physician's overall assessment of psoriasis focusing on plaque thickness/induration, erythema, and scaling.

In both studies, subjects in all treatment groups had a median baseline PASI score ranging from approximately 17 to 18. Baseline PGA score was marked or severe in 44% of subjects in STUDY 1 and 40% of subjects in STUDY 2. Approximately two-thirds of all subjects had received prior phototherapy, 69% had received either prior conventional systemic or biologic therapy for the treatment of psoriasis, with 56% receiving prior conventional systemic therapy and 43% receiving prior biologic therapy. A total of 28% of study subjects had a history of psoriatic arthritis.

Clinical Response:
The results of STUDY 1 and STUDY 2 are upon examination of age, gender, and race subgroups did not identify differences in response to Stelara among these subgroups. In subjects who weighed < 100 kg, response rates were similar with both the 45 mg and 90 mg doses; however, in subjects who weighed > 100 kg, higher response rates were seen with 90 mg dosing compared with 45 mg dosing.

Subjects in STUDY 1 were evaluated through week 52. At week 40, those who were PASI 75 responders at both weeks 28 and 40 were re-randomized to either continued dosing of Stelara or to withdrawal of therapy. At week 52, 89% (144/162) of subjects re-randomized to Stelara treatment were PASI 75 responders compared with 63% (100/159) of subjects re-randomized to placebo (treatment withdrawal after week 28 dose).

Psoriatic Arthritis (PsA)
The safety and efficacy of STELARA® was assessed in 927 patients (PsA STUDY 1, n=615; PsA STUDY 2, n=312), in two randomized, double-blind, placebo-controlled studies in adult patients 18 years of age and older with active PsA (≥5 swollen joints and ≥5 tender joints) despite non-steroidal anti-inflammatory (NSAID) or disease modifying antirheumatic (DMARD) therapy. Patients in these studies had a diagnosis of PsA for at least six months. Patients with each subtype of PsA were enrolled, including polyarticular arthritis with the absence of rheumatoid nodules (39%), spondylitis with peripheral arthritis (28%), asymmetric peripheral arthritis (21%), distal interphalangeal involvement (12%) and arthritis mutilans (0.5%). Over 70% and 40% of the patients, respectively, had enthesitis and dactylitis at baseline.

Patients were randomized to receive treatment with STELARA® 45 mg, 90 mg, or placebo subcutaneously at weeks 0 and four followed by every 12 weeks (q12w) dosing. Approximately 50% of patients continued on stable doses of MTX (≤25 mg/week). The primary endpoint was the percentage of patients achieving ACR 20 response at week 24.

In PsA STUDY 1 and PsA STUDY 2, 80% and 86% of the patients, respectively, had been previously treated with DMARDs. In PsA STUDY 1, previous treatment with anti-tumor necrosis factor (TNF)-α agent was not allowed. In PsA STUDY 2, 58% (n=180) of the patients had been previously treated with an anti-TNFα agent, of whom over 70% had discontinued their anti-TNFα treatment for lack of efficacy or intolerance at any time.

Clinical Response:
In both studies, a greater proportion of patients achieved ACR 20, ACR 50 and PASI 75 response in the STELARA® 45 mg and 90 mg groups compared to placebo at week 24. ACR 70 responses were also higher in the STELARA® 45 mg and 90 mg groups, although the difference was only numerical (p=NS) in Study 2. Responses were similar in patients regardless of prior TNFα exposure. An improvement in enthesitis and dactylitis scores was observed in each STELARA® group compared with placebo at week 24.

Physical Function:
STELARA® treated patients showed improvement in physical function compared to patients treated with placebo as assessed by HAQ-DI at week 24. In both studies, the proportion of HAQ-DI responders (≥0.3 improvement in HAQ-DI score) was greater in the STELARA® 45 mg and 90 mg groups compared to placebo at week 24.

Actemra (tocilizumab)
Actemra (tocilizumab) is an interleukin-6 (IL-6) receptor inhibitor indicated for treatment of rheumatoid arthritis (RA). Those eligible for treatment of RA with Actemra must be diagnosed with moderately-to severely active rheumatoid arthritis that have had an inadequate response to one or more TNF antagonist therapies. Actemra may be used alone on in combination with methotrexate (MTX) or other DMARDS. The drug is administered intravenously for a single drip infusion over one hour and should not be given as a bolus or push. Recommended adult dosing is every four weeks. Whether used with MTX, other DMARDS or alone, recommended starting dose is 4mg/kg followed by an increase to 8mg/kg based on clinical response. This drug does come the BLACK BOX warning. When preparing the medication for administration, it must be prepared by a healthcare professional using aseptic technique.

The efficacy and safety of Actemra was assessed in five randomized, double-blind, multicenter studies in patients > 18 years of age with active rheumatoid arthritis diagnosed according to American College of Rheumatology (ACR) criteria. Actemra was given intravenously every four weeks as monotherapy (Study I), in combination with MTX (Studies II and III) or other DMARDS (Study IV), or in combination with MTX in those with an inadequate response to TNF antagonizes (StudyV). The studies showed Actemra, alone or in combination with MTX or other DMARDs, significantly reduced the signs and symptoms of rheumatoid arthritis compared with DMARDS alone.

On April 18, 2011, the FDA approved the use of Actemra for the treatment of active Systemic Juvenile Idiopathic Arthritis (SJIA) in patients two years of age and older. Actemra can be given alone or in combination with methotrexate in patients with SJIA. Actemra is the first medicine approved by the FDA for the treatment of SJIA, a rare and severe form of arthritis affecting children. SJIA has the worst long-term prognosis of all types of childhood arthritis. SJIA affects about 10 to 20 percent of children with juvenile idiopathic arthritis (JIA), with the peak onset between 18 months and two years, although the disease can persist into adulthood.

This approval was based on positive data from a Phase III study known as TENDER. The results showed that 85% (64/75) of children with SJIA receiving Actemra experienced a 30% improvement (JIA ACR30) in the signs and symptoms of SJIA and an absence of fever after 12 weeks of therapy, compared with 24% (9/37) of children receiving placebo ($p<0.0001$). Additional results from the TENDER study, a randomized, double-blind, Phase III study in 112 patients showed significantly more children who received Actemra had improvements in SJIA signs and symptoms. In the study, 71% (53/75) of children treated with Actemra achieved a JIA ACR70 at week 12 compared with 8% (3/37) of those receiving placebo ($p<0.0001$).

Actemra (tocilizumab) was re-evaluated as a treatment to be used after failure of DMARDS. The study showed positive responses and the requirement that a TNF had to be failed first was removed.

SIMPONI ARIA (golimumab)
The following information was obtained from the prescribing information for SIMPONI ARIA.

The efficacy and safety of SIMPONI ARIA were evaluated in one multicenter, randomized, double-blind, controlled trial (Trial 1) in 592 patients ≥ 18 years of age with moderately to severely active RA despite concurrent MTX therapy and had not previously been treated with a biologic TNF-blocker. Patients were diagnosed according to the American College of Rheumatology (ACR) criteria, at least three months prior to administration of study agent and were required to have at least six swollen and six tender joints. Patients were randomized to receive either SIMPONI ARIA 2mg/kg (n=395) or placebo (n=197) over a 30 minute intravenous infusion at weeks 0, 4, and every eight weeks thereafter in addition to their weekly maintenance MTX dose (15 – 25 mg/kg). All patients receiving placebo + MTX received SIMPONI ARIA + MTX after week 24, but the trial remained blinded until all patients had completed 52 weeks of treatment. Efficacy data were collected and analyzed through week 52. Patients were allowed to continue stable doses of concomitant low dose corticosteroids

(equivalent to ≤ 10 mg of prednisone a day) and/or NSAIDs and patients may have received oral MTX during the trials. The use of other DMARDs including cytotoxic agents or other biologics was prohibited.

The primary endpoint in Trial 1 was the percentage of patients achieving an ACR 20 response at week 14. In Trial 1, the majority of subjects were women (82%) and were Caucasian (81%) with a median age of 52 years and a median weight of 70 kg. Median disease duration was 4.7 years, and 50% of the patients used at least one DMARD other than MTX in the past. At baseline, 81% of patients received concomitant NSAIDs and 81% of patients received low dose corticosteroids (equivalent to ≤ 10 mg of prednisone a day). The median baseline DAS28-CRP was 5.9 and the median van der Heijde-Sharp score at baseline was 28.5.

Results from the trial revealed 59 percent (n=231/395) of patients receiving treatment with SIMPONI ARIA plus methotrexate versus 25% of patients receiving placebo plus methotrexate (n=49/197) (a difference with 95% CI 25.9, 41.4) experienced significant improvements in signs and symptoms at week 14, as demonstrated by at least 20% improvement in American College of Rheumatology criteria (ACR 20), the study's primary endpoint. A higher proportion of patients receiving SIMPONI ARIA plus methotrexate achieved at least a 50% improvement in ACR criteria (ACR 50) compared with patients receiving placebo plus methotrexate at week 14 (30% versus 9%, respectively, a difference with 95% CI 15.3, 27.2). Significant improvements in ACR 20 were observed as early as week 2, after a single SIMPONI ARIA infusion, as 33% of patients achieved an ACR 20 response versus 12% of patients receiving placebo. Radiographic progression of the hands and feet were assessed by the change from baseline in van der Heijde-Sharp (vdH-S) scores, an X-ray measure of joint destruction, including joint erosion and joint space narrowing in which higher scores indicate greater structural damage. At week 24, patients receiving SIMPONI ARIA plus methotrexate had a mean change in total vdH-S score of 0.03 from baseline, compared with a mean change of 1.09 in the placebo plus methotrexate group (P<0.001). At week 52, the mean change in total vdH-S score from baseline was 0.13 in SIMPONI ARIA treated patients versus 1.20 in placebo patients who crossed over to SIMPONI ARIA at either week 16 or 24.

Physical function was assessed by the disability index of the Health Assessment Questionnaire (HAQ-DI). At week 14, the SIMPONI ARIA + MTX group showed greater mean improvement in the HAQ-DI compared with placebo + MTX (0.5 compared to 0.2; 95% CI [0.2, 0.4]).

Key Words:

Remicade, infliximab, Crohn's disease, rheumatoid arthritis, ankylosing spondylosis, psoriatic arthritis, Ulcerative colitis, UC, Behçet's disease, Behçet's syndrome, Wegener's Granulomatosis, WG, vasculitis, sarcoidosis, refractory sarcoidosis, Abatacept, Orencia, rheumatoid arthritis, disease modifying anti-rheumatic drug DMARD, tumor necrosis factor, TNF, antagonist, pediatric Crohn's disease, psoriasis, polyarticular juvenile idiopathic arthritis, juvenile idiopathic arthritis, JIA, Cimzia, certolizumab pegol, Stelara, ustekinumab, plaque psoriasis, Actemra, tocilizumab, hidradenitis suppurativa, systemic juvenile idiopathic arthritis, SJIA, SIMPONI ARIA, golimumab, ankylosing spondylitis

Approved by Governing Bodies:

Remicade received FDA approval for treatment of Crohn's Disease and Rheumatoid Arthritis
December 20, 2004—Received FDA approval for ankylosing spondylitis, Remicade
May 13, 2005—Received FDA approval for reducing signs and symptoms of active arthritis in patients with psoriatic arthritis, Remicade
September 15, 2005—Received FDA approval for the treatment of ulcerative colitis (UC); Remicade
Abatacept received FDA approval December 23, 2005
Remicade received FDA approval for treatment of Pediatric Crohn's disease- May 19, 2006
Remicade received FDA approval for treatment of chronic severe plaque psoriasis- September 26, 2006
Abatacept received FDA approval for treatment of moderately to severely active polyarticular juvenile idiopathic arthritis in pediatric patients 6 years of age and older-April 8, 2008
Cimzia (certolizumab pegol) received FDA approval for moderately to severely active Crohn's disease on April 22, 2008
Cimzia (certolizumab pegol) received FDA approval for adults for active rheumatoid arthritis on May 14, 2009
Stelara (ustekinumab) received FDA approval for adults for moderate to severe plaque psoriasis on September 25, 2009.
Actemra (tocilizumab) received FDA approval for the treatment of rheumatoid arthritis on January 10, 2010.
Actemra (tocilizumab) received FDA approval for the treatment of systemic juvenile idiopathic arthritis (SJIA) on April 18, 2011.
Remicade (infliximab) received FDA approval for the treatment of ulcerative colitis in children older than 6 years old on September 23, 2011.
Actemra (Tocilizumab) received FDA approval for rheumatoid arthritis in patients who had failed DMARDs on October 11, 2012.
SIMPONI ARIA received FDA approval for the treatment of adults with moderately to severely active rheumatoid arthritis in combination with methotrexate on July 18, 2013.
Stelara (ustekinumab) received FDA approval for treatment of adult patients with moderate-to-severe psoriatic arthritis on September 23, 2013.
Cimzia (certolizumab pegol) received FDA approval for the treatment of adults with active psoriatic arthritis on September 30, 2013.
Cimzia (certolizumab pegol) received FDA approval for the treatment of adults with ankylosing spondylitis on October 18, 2013.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply
FEP contracts: FEP does not consider investigational if FDA approved and will be reviewed for medical necessity. Special benefit consideration may apply. Refer to member's benefit plan.

Lowe's Precertification Requirement—**Effective for dates of service on or after February 1, 2010** please contact Care Continuum at 866-240-4734 or fax the prescription with accompanying clinical information to 877-540-6223 for precertification. (This Blue Cross and Blue Shield of Alabama's medical policy does not apply for Lowe's members for dates of service on or after February 1, 2010. This policy was in effect for Lowe's prior to February 1, 2010).
Pre-certification/Pre-determination requirements: Not applicable

Current Coding:

HCPCS codes:

J0129	Injection, Abatacept, 10 mg
J0717	Injection, certolizumab pegol, 1 mg (code may be used for Medicare when drug administered under the direct supervision of a physician, not for use when drug is self-administered) **(effective 01/01/2014)**
J1602	Injection, golimumab, 1 mg, for intravenous use **(effective 01/01/2014)**
J1745	Injection, infliximab, 10mg
J3262	Injection, tocilizumab, 1 mg
J3357	Injection, ustekinumab, 1 mg
J3590	Unclassified biologics

Previous Coding

HCPCS codes:

C9249	Injection, Certolizumab Pegol, 1 mg **(deleted 01/01/2010)**
J0718	Injection, Certolizumab Pegol, 1 mg **(deleted 12/31/2013)**

References:

1. Aaltonen KJ, Virkki LM, Malmivaara A et al. Systematic review and meta-analysis of the efficacy and safety of existing TNF blocking agents in treatment of rheumatoid arthritis. PLoS One 2012; 7(1):e30275.
2. Akobeng AK. Crohn's disease: current treatment options. Arch Dis Child 2008; 93(9):787-92.
3. Alhusayen R, Shear NH. Pharmacologic interventions for hidradenitis suppurativa: what does the evidence say? Am J Clin Dermatol 2012; 13(5):283-91.
4. Al-Rayes H, Al-Swailem R, Al-Balawi M et al. Safety and efficacy of infliximab therapy in active behcet's uveitis: an open-label trial. Rheumatol Int 2008; 29(1):53-7.
5. American College of Rheumatology. Model Biologics Policy 2011. Available online at: http://www.rheumatology.org/practice/office/insurance/model_biologics_policy.pdf. Last accessed August, 2012.
6. Antoni CE, Kavanaugh A, Kirkham B et al. Sustained benefits of infliximab therapy for dermatologic and articular manifestations of psoriatic arthritis: results from the infliximab

multinational psoriatic arthritis controlled trial (IMPACT). Arthritis Rheum 2005; 52(4):1227-36.
7. Arida A, Fragiadaki K, Giavri E et al. Anti-TNF agents for Behcet's disease: analysis of published data on 369 patients. Semin Arthritis Rheum 2011; 41(1):61-70.
8. Askling J, Fahrbach K, Nordstrom B et al. Cancer risk with tumor necrosis factor alpha (TNF) inhibitors: meta-analysis of randomized controlled trials of adalimumab, etanercept, and infliximab using patient level data. Pharmacoepidemiology and drug safety 2011; 20(2):119-30.
9. Atteno M, Peluso R, Costa L et al. Comparison of effectiveness and safety of infliximab, etanercept, and adalimumab in psoriatic arthritis patients who experienced an inadequate response to previous disease-modifying antirheumatic drugs. Clin Rheumatol 2010; 29(4):399-403.
10. Baranauskaite A, Raffayova H, Kungurov NV et al. Infliximab plus methotrexate is superior to methotrexate alone in the treatment of psoriatic arthritis in methotrexate-naive patients: the RESPOND study. Ann Rheum Dis 2012; 71(4):541-8.
11. Barker J, Hoffmann M, Wozel G et al. Efficacy and safety of infliximab vs. methotrexate in patients with moderate-to-severe plaque psoriasis: results of an open-label, active-controlled, randomized trial (RESTORE1). Br J Dermatol 2011; 165(5):1109-17.
12. Barkham N, Keen HI, Coates LC et al. Clinical and imaging efficacy of infliximab in HLA-B27-Positive patients with magnetic resonance imaging-determined early sacroiliitis. Arthritis Rheum 2009; 60(4):946-54.
13. Bartolucci P, et al. Efficacy of the anti-TNF-alpha antibody infliximab against refractory systemic vasculitides: An open pilot study on 10 patients, Rheumatology, October 2002; 41(10): 1126-32.
14. Behm BW, Bickston SJ. Tumor necrosis factor-alpha antibody for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev 2008; (1):CD006893.
15. Blok JL, van Hattem S, Jonkman MF et al. Systemic therapy with immunosuppressive agents and retinoids in hidradenitis suppurativa: a systematic review. Br J Dermatol 2013; 168(2):243-52.
16. Blue Cross Blue Shield Association. Off-label uses of tumor necrosis factor inhibitors in ankylosing spondylitis, ulcerative colitis, and psoriasis, June 23, 2003, Vol. 20, No. 2.
17. Brandt Jan, et al. Successful short-term treatment of severe undifferentiated spondyloarthropathy with the anti-tumor necrosis factor-α monoclonal antibody infliximab, The Journal of Rheumatology 2002: 29; 118-122.
18. Brandt Jan, et al. Successful treatment of active ankylosing spondylitis with the anti-tumor necrosis factor and monoclonal antibody infliximab, Arthritis and Rheumatism, June 2000, Vol. 43, No. 6, pp. 1346-1352.
19. Braun J, Brandt J, Listing J, et al. Treatment of active ankylosing spondylitis with infliximab: A randomized controlled multicenter trial, The Lancet, April 2002, Vol. 359.
20. Bristol-Myers Squibb, Inc. Orencia (abatacept) Prescribing Information. April 2008.
21. Bryan S, Andronis L, Hyde C et al. Infliximab for the treatment of acute exacerbations of ulcerative colitis. Health Technol Assess 2010; 14 Suppl 1:9-15.
22. Burns JC, Best BM, Mejias A et al. Infliximab treatment of intravenous immunoglobulin-resistant Kawasaki disease. J Pediatr 2008; 153(6):833-8.
23. Burns JC, Mason WH, Hauger SB et al. Infliximab treatment for refractory Kawasaki syndrome. J Pediatr 2005; 146(5):662-7.

24. Callhoff J, Weiss A, Zink A et al. Impact of biologic therapy on functional status in patients with rheumatoid arthritis--a meta-analysis. Rheumatology (Oxford) 2013.
25. Canadian Agency for Drugs and Technologies in Health; HTA Technology Report. Infliximab and etanercept in rheumatoid arthritis: systematic review of long-term effectiveness, safety, and cost-effectiveness. Issue 85. March 2007. Available online at: http://cadth.ca/media/pdf/318A_Anti-TNF_tr_e.pdf. Last accessed November 18, 2011.
26. Cassidy JT, Levinson JE, Bass JC et al. A study of classification criteria for a diagnosis of juvenile rheumatoid arthritis. Arthritis Rheum 1986; 29:274-81.
27. Chang KH, Burke JP, Coffey JC. Infliximab versus cyclosporine as rescue therapy in acute severe steroid-refractory ulcerative colitis: a systematic review and meta-analysis. Int J Colorectal Dis 2013; 28(3):287-93.
28. Chey William Y, et al. Infliximab for refractory ulcerative colitis, The American Journal of Gastroenterology, August 2001, Vol. 96, No. 8, pp. 2373-2381.
29. Chey William Y. Infliximab for patients with refractory ulcerative colitis, Inflammatory Bowel Diseases, May 2001, Vol. 7, Suppl 1, pp. S30-S33.
30. Cimzia prescribing information, www.cimzia.com/pi.asp.
31. Colombel JF, Sandborn WJ, Reinisch W et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. The New England journal of medicine 2010; 362(15):1383-95.
32. Cordero-Coma M, Yilmaz T, Onal S. Systematic review of anti-tumor necrosis factor-alpha therapy for treatment of immune-mediated uveitis. Ocul Immunol Inflamm 2013; 21(1):19-27.
33. Costa J, Magro F, Caldeira D et al. Infliximab Reduces Hospitalizations and Surgery Interventions in Patients With Inflammatory Bowel Disease: A Systematic Review and Meta-analysis. Inflamm Bowel Dis 2013; 19(10):2098-110.
34. Couriel DR, Saliba R, de Lima M et al. A phase III study of infliximab and corticosteroids for the initial treatment of acute graft-versus-host disease. Biol Blood Marrow Transplant 2009; 15(12):1555-62.
35. de Menthon M, Cohen P, Pagnoux C et al. Infliximab or rituximab for refractory Wegener's granulomatosis: long-term follow up. A prospective randomised multicentre study on 17 patients. Clin Exp Rheumatol 2011; 29(1 Suppl 64):S63-71.
36. D'Haens G, Baert F, van Assche G et al. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. Lancet 2008; 371(9613):660-7.
37. Donahue KE JD, Hansen RA, et al. Drug Therapy for Psoriatic Arthritis in Adults: Update of a 2007 Report. Comparative Effectiveness Review No. 54. Agency for Healthcare Research and Quality. AHRQ Publication No. 12-EHC024-EF. April 2012. Available online at: www.effectivehealthcare.ahrq.gov/reports/final/cfm. Last accessed August, 2012.
38. Doty John, Masur Joseph E and Judson Marc A. Treatment of sarcoidosis with infliximab, Chest, March 2005, Vol. 127, No. 3.
39. Dretzke J, Edlin R, Round J et al. A systematic review and economic evaluation of the use of tumour necrosis factor-alpha (TNF-alpha) inhibitors, adalimumab and infliximab, for Crohn's disease. Health Technol Assess 2011; 15(6):1-244.
40. Fenix-Caballero S, Alegre-del Rey EJ, Castano-Lara R et al. Direct and indirect comparison of the efficacy and safety of adalimumab, etanercept, infliximab and golimumab in psoriatic arthritis. J Clin Pharm Ther 2013; 38(4):286-93.

41. Gallego-Galisteo M, Villa-Rubio A, Alegre-del Rey E et al. Indirect comparison of biological treatments in refractory rheumatoid arthritis. J Clin Pharm Ther 2012; 37(3):301-7.
42. Giannini EH, Brewer EJ, Kuzmina N et al. Methotrexate in resistant juvenile rheumatoid arthritis. Results o the U.S.A.-U.S.S.R. double-blind, placebo-controlled trial. The Pediatric Rheumatology Collaborative Study Group and The Cooperative Children's Study Group. N Engl J Med 1992; 326:1043-9.
43. Giannini EH, Ruperto N, Ravelli A, et al. Preliminary definition of improvement in juvenile arthritis. Arthritis Theum 1997; 40:1202-9.
44. Gottlieb AB, Evans R, Li S et al. Infliximab induction therapy for patients with severe plaque-type psoriasis: a randomized, double-blind, placebo-controlled trial. J Am Acad Dermatol 2004; 51(4):534-42.
45. Grant A, Gonzalez T, et al. Infliximab therapy for patients with moderate to severe hidradenitis suppurative: A randomized, double-blind, placebo-controlled crossover trial. J Am Acad Dermatol 2010; 62: 205-217.
46. Hanauer Stephen B, Geagan Brian G, et al. Maintenance infliximab for Crohn's disease: The ACCENT I randomised trial, The Lancet, May 2002, Vol. 359, No. 9317, pp. 1541-1549.
47. Hanauer SB, Wagner CL, Bala M et al. Incidence and importance of antibody responses to infliximab after maintenance or episodic treatment in Crohn's disease. Clin Gastroenterol Hepatol 2004; 2:542-53.
48. Harrison ML, Obermueller E, Maisey NR et al. Tumor necrosis factor alpha as a new target for renal cell carcinoma: two sequential phase II trials of infliximab at standard and high dose. J Clin Oncol 2007; 25(29):4542-9.
49. Hernandez-Rodriguez J, Cid MC, Lopez-Soto A, et al. Treatment of polymyalgia rheumatica: a systematic review. Arch Intern Med 2009; 169(20):1839-50.
50. Hoffman GS, Cid MC, Rendt-Zagar KE et al. Infliximab for maintenance of glucocorticosteroid-induced remission of giant cell arteritis: a randomized trial. Ann Intern Med 2007; 146(9):621-30.
51. Hoffman GS, Merkel PA, Brassington RD, et al. Utility of anti-TNF therapy in Takayasu's arteritis. Presentation 1101.
52. Hommes DW, Erkelens W, Ponsioen C et al. A double-blind, placebo-controlled, randomized study of infliximab in primary sclerosing cholangitis. J Clin Gastroenterol 2008; 42(5):522-6.
53. Hyams J, Crandall W, Kugathasan S et al. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. Gastroenterology 2007; 132(3):863-73; quiz 1165-6.
54. Hyams J, Walters TD, Crandall W et al. Safety and efficacy of maintenance infliximab therapy for moderate-to-severe Crohn's disease in children: REACH open-label extension. Current medical research and opinion 2011; 27(3):651-62.
55. Hyams JS, Damaraju L, Blank M, et al. A randomized multicenter, open-label phase 3 study to evaluate the safety and efficacy of infliximab in pediatric patients with moderate to severe ulcerative colitis. Gastroenterology. 2011; 140(5, Suppl. 1):S-124-S-125.
56. Hyams JS, Lerer T, Griffiths A, et al. Outcome following infliximab therapy in children with ulcerative colitis. Am J Gastroenterol. 2010; 105:1430-1436.

57. Hyde C, Bryan S, Juarez-Garcia A et al. Infliximab for the treatment of ulcerative colitis. Health Technol Assess 2009; 13 Suppl 3:7-11.
58. Jatoi A, Ritter HL, Dueck A et al. A placebo-controlled, double-blind trial of infliximab for cancer-associated weight loss in elderly and/or poor performance non-small cell lung cancer patients (N01C9). Lung Cancer 2010; 68(2):234-9.
59. Josselin L, Mahr A, Cohen P et al. Infliximab efficacy and safety against refractory systemic necrotising vasculitides: long-term follow-up of 15 patients. Ann Rheum Dis 2008; 67(9):1343-6.
60. Judson MA, Baughman RP, Costabel U et al. Efficacy of infliximab in extrapulmonary sarcoidosis: results from a randomised trial. Eur Respir J 2008; 31(6):1189-96.
61. Kemper AR CR, Sanders GD, et al. Disease-Modifying Antirheumatic Drugs (DMARDs) in Children with Juvenile Idiopathic Arthritis. Comparative Effectiveness Review No. 28. AHRQ Publication No. 11-EHC039-EF. Rockville, MD: Agency for Healthcare Research and Quality. August 2011. Available online at: www.effectivehealthcare.ahrq.gov/reports/final.cfm. Last accessed August, 2012.
62. Koninckx PR, Craessaerts M, Timmerman D et al. Anti-TNF-alpha treatment for deep endometriosis-associated pain: a randomized placebo-controlled trial. Hum Reprod 2008; 23(9):2017-23.
63. Kopylov U, Ben-Horin S, Zmora O et al. Anti-tumor necrosis factor and postoperative complications in Crohn's disease: systematic review and meta-analysis. Inflamm Bowel Dis 2012. [Epub ahead of print]
64. Kozuch PL, Hanauer SB. Treatment of inflammatory bowel disease: a review of medical therapy. World J Gastroenterol 2008; 14(3):354-77.
65. Kruithof E, Van den Bosch F, et al. Repeated infusions of infliximab, a chimeric anti-TNFα monoclonal antibody, in patients with active spondyloarthropathy: one year follow up, Ann Rheum Disease 2002; 61: 207-212.
66. Lamprecht P, et al. Effectiveness of TNF-alpha blockade with infliximab in refractory Wegener's granulomatosis, Rheumatology, November 2002; 41(11): 1303-7.
67. Lebwohl, B and Sapadin AN. Infliximab for the treatment of hidradenitis suppurativa. J Am Acad Dermatol 2003; 49: S275-276.
68. Lee S CC, Limone B, Kaur R, White CM, Kluger J, Sobieraj DM. . Biologic and Nonbiologic Systemic Agents and Phototherapy for Treatment of Chronic Plaque Psoriasis. Comparative Effectiveness Review No. 85. (Prepared by the University of Connecticut/Hartford Hospital Evidence-based Practice Center under Contract No. 290-2007-10067-I.) AHRQ Publication No. 12(13)-EHC144-EF. Rockville, MD: Agency for Healthcare Research and Quality. November 2012.
69. Lichtenstein GR, Abreu MT, Cohen R et al. American Gastroenterological Association Institute medical position statement on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease. Gastroenterology 2006; 130(3):935-9.
70. Lichtenstein GR, Rutgeerts P, Sandborn WJ et al. A pooled analysis of infections, malignancy, and mortality in infliximab- and immunomodulator-treated adult patients with inflammatory bowel disease. Am J Gastroenterol 2012; 107(7):1051-63.
71. Lin J, Ziring D, Desai S et al. TNF-alpha blockade in human diseases: an overview of efficacy and safety. Clin Immunol 2008; 126(1):13-30.

72. Lopez-Olivo MA, Tayar JH, Martinez-Lopez JA et al. Risk of malignancies in patients with rheumatoid arthritis treated with biologic therapy: a meta-analysis. JAMA 2012; 308(9):898-908.
73. Lovell DJ, Giannini EH, Reiff A et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. N Engl J Med 2000; 342:763-9.
74. Lovell DJ, Ruperto N, Goodman S et al. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. N Engl J Med 2008; 359:810-20.
75. Loza MJ, Brodmerkel C, Du Bois RM et al. Inflammatory profile and response to anti-tumor necrosis factor therapy in patients with chronic pulmonary sarcoidosis. Clin Vaccine Immunol 2011; 18(6):931-9.
76. Lv D, Song H, Shi G. Anti-TNF-alpha treatment for pelvic pain associated with endometriosis. Cochrane Database Syst Rev 2010; (3):CD008088.
77. Lucka TC, Pathirana D, Sammain A, et al. Efficacy of systemic therapies for moderate-to-severe psoriasis: a systematic review and meta-analysis of long-term treatment. J Eur Acad Dermatol Venereol 2012.
78. Maas DW, Westendorp RG, Willems JM et al. TNF-alpha antagonist infliximab in the treatment of depression in older adults: results of a prematurely ended, randomized, placebo-controlled trial. J Clin Psychopharmacol 2010; 30(3):343-5.
79. Machado MA, Barbosa MM, Almeida AM et al. Treatment of ankylosing spondylitis with TNF blockers: a meta-analysis. Rheumatol Int 2013; 33(9):2199-213.
80. Malottki K, Barton P, Tsourapas A, et al. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a tumour necrosis factor inhibitor: a systematic review and economic evaluation. Health Technol Assess 2011; 15(14):1-278.
81. Maneiro JR, Salgado E, Gomez-Reino JJ et al. Efficacy and Safety of TNF Antagonists in Sarcoidosis: Data from the Spanish Registry of Biologics BIOBADASER and a Systematic Review. Semin Arthritis Rheum 2012; 42(1):89-103.
82. McLeod C, Bagust A, Boland A, et al. Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis: a systematic review and economic evaluation. Health Technol Assess 2007; 11(28):1-158, iii-iv.
83. Mekkes JR and Bos JD. Long-term efficacy of a single course of infliximab in hidradenitis suppurativa. British J Dermatol, September 2008; 159(3): 761-763.
84. Menter A, Gottlieb A, Feldman SR et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. J Am Acad Dermatol 2008; 58(5):826-50.
85. Migliore A, Broccoli S, Bizzi E et al. Indirect comparison of the effects of anti-TNF biological agents in patients with ankylosing spondylitis by means of a mixed treatment comparison performed on efficacy data from published randomised, controlled trials. J Med Econ 2012; 15(3):473-80.
86. Moller DR. Treatment of sarcoidosis – from a basic science point of view, Journal of Internal Medicine, January 2003; 253(1): 31-40.
87. Moulis G, Sommet A, Bene J et al. Cancer risk of anti-TNF-alpha at recommended doses in adult rheumatoid arthritis: a meta-analysis with intention to treat and per protocol analyses. PLoS One 2012; 7(11):e48991.

88. Niccoli L, Nannini C, Benucci M et al. Long-term efficacy of infliximab in refractory posterior uveitis of Behcet's disease: a 24-month follow-up study. Rheumatology (Oxford) 2007; 46(7):1161-4.
89. Nussenblatt RB, Byrnes G, Sen HN et al. A randomized pilot study of systemic immunosuppression in the treatment of age-related macular degeneration with choroidal neovascularization. Retina 2010; 30(10):1579-87.
90. Pavelka K, Jarosova K, Suchy D et al. Increasing the infliximab dose in rheumatoid arthritis patients: a randomised, double blind study failed to confirm its efficacy. Annals of the rheumatic diseases 2009; 68(8):1285-9.
91. Peyrin-Biroulet L, Deltenre P, de Suray N et al. Efficacy and safety of tumor necrosis factor antagonists in Crohn's disease: meta-analysis of placebo-controlled trials. Clin Gastroenterol Hepatol 2008; 6(6):644-53.
92. Phumethum V, Jamal S, Johnson SR. Biologic therapy for systemic sclerosis: a systematic review. The Journal of rheumatology 2011; 38(2):289-96.
93. Raison CL, Rutherford RE, Woolwine BJ et al. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. JAMA Psychiatry 2013; 70(1):31-41.
94. Rambhatla PV, Lim HW, Hamzavi I. A systematic review of treatments for hidradenitis suppurativa. Arch Dermatol 2012; 148(4):439-46.
95. Ramos-Casals M, Tzioufas AG, Stone JH et al. Treatment of primary Sjogren syndrome: a systematic review. JAMA 2010; 304(4):452-60.
96. Ravelli A, Martini A. Juvenile idiopathic arthritis. Lancet 2007; 369:767-78.
97. Regan Michael J, Hellmann David B, and Stone John H. Treatment of Wegener's granulomatosis, Rheumatic Diseases Clinics of North America, November 2001, Vol. 27, No. 4.
98. Reich K, Burden AD, Eaton JN et al. Efficacy of biologics in the treatment of moderate to severe psoriasis: a network meta-analysis of randomized controlled trials. Br J Dermatol 2012; 166(1):179-88.
99. Reinisch W, Sandborn WJ, Rutgeerts P et al. Long-term infliximab maintenance therapy for ulcerative colitis: the ACT-1 and -2 extension studies. Inflamm Bowel Dis 2012; 18(2):201-11.
100. Remicade® (Infliximab prescribing information, www.remicade.com.
101. Ren L, Li J, Luo R et al. Efficacy of Antitumor Necrosis Factor(alpha) Agents on Patients With Ankylosing Spondylitis. Am J Med Sci 2013.
102. Ringold S. Juvenile idiopathic arthritis. JAMA, October 2005, Vol. 294, No. 13.
103. Roberts SD. Refractory sarcoidosis responding to infliximab, Chest, November 2003; 124(5): 2028-31.
104. Roche Media Releases. FDA approved Actemra for the treatment of Systemic Juvenile Idiopathic Arthritis (SJIA). April 2011, www.roche.com/media/media_releases.htm.
105. Rodgers M, Epstein D, Bojke L et al. Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis: a systematic review and economic evaluation. Health Technol Assess 2011; 15(10): i-xxi, 1-329.
106. Rosenbach M, Hsu S, Korman NJ, et al. Treatment of erythrodermic psoriasis: from the medical board of the National Psoriasis Foundation. J Am Acad Dermatol 2010; 62(4):655-62.

107. Rosenfeld G, Qian H, Bressler B. The risks of post-operative complications following pre-operative infliximab therapy for Crohn's disease in patients undergoing abdominal surgery: A systematic review and meta-analysis. J Crohns Colitis 2013.
108. Ruddy: Kelley's Textbook of Rheumatology, 6th ed., 2001. W. B. Saunders Company.
109. Ruperto N, Lovell DJ, Cuttica R et al. Long-term efficacy and safety of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis: findings from an open-label treatment extension. Annals of the rheumatic diseases 2010; 69(4):718-22.
110. Ruperto N, Murray KJ, Gerloni V et al. A randomized trial of parenteral methotrexate comparing an intermediate dose with a higher dose in children with juvenile idiopathic arthritis who failed to respond to standard dose of methotrexate. Arthritis Rheum 2004; 50:2191-201.
111. Ruperto N, Lovell DJ, Cuttica R et al. A randomized, placebo-controlled trial of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis. Arthritis Rheum 2007; 56:3096-106.
112. Ruperto N, Lovell DJ, Quartier P et al. Abatacept in children with juvenile idiopathic arthritis: a randomized, double-blind, placebo-controlled withdrawal trial. Lancet 2008; 372:383-91.
113. Ruperto N, Ravelli A, Falcini F et al. Performance of the preliminary definition of improvement in juvenile chronic arthritis patients treated with methotrexate. Italian Pediatric Rheumatology Study Group. Ann Rheum Dis 1998; 57:38-41.
114. Rutgeerts P, Sandborn WJ, Feagan BG et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med 2005; 353(23):2462-76.
115. Salvarani C, Macchioni P, Manzini C et al. Infliximab plus prednisone or placebo plus prednisone for the initial treatment of polymyalgia rheumatica: a randomized trial. Ann Intern Med 2007; 146(9):631-9.
116. Sands Bruce E, et al. Infliximab in the treatment of severe, steroid-refractory ulcerative colitis: A pilot study, Inflammatory Bowel Diseases, May 2001, Vol. 7, No. 2, pp. 83-88.
117. Schatteman L, Gyselbrecht L, De Clercq L et al. Treatment of refractory inflammatory monoarthritis in ankylosing spondylitis by intraarticular injection of infliximab. J Rheumatol 2006; 33(1):82-5.
118. Schiff M, Keiserman M, Codding C et al. Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. Ann Rheum Dis 2008; 67(8):1096-103.
119. Schmitz S, Adams R, Walsh CD et al. A mixed treatment comparison of the efficacy of anti-TNF agents in rheumatoid arthritis for methotrexate non-responders demonstrates differences between treatments: a Bayesian approach. Annals of the rheumatic diseases 2011.
120. Sfikakis PP, Grigoropoulos V, Emfietzoglou I et al. Infliximab for diabetic macular edema refractory to laser photocoagulation: a randomized, double-blind, placebo-controlled, crossover, 32-week study. Diabetes Care 2010; 33(7):1523-8.
121. Sharma P, Kumar A, Sharma BC et al. Infliximab monotherapy for severe alcoholic hepatitis and predictors of survival: an open label trial. J Hepatol 2009; 50(3):584-91.
122. Shenoi S, Wallace CA. Tumor necrosis factor inhibitors in the management of juvenile idiopathic arthritis: an evidence-based review. Paediatric drugs 2010; 12(6):367-77.

123. Singh G, Athreya BH, Fries JF et al. Measurement of health status in children with juvenile rheumatoid arthritis. Arthritis Rheum 1994; 37:1761-9.
124. Singh JA, Christensen R, Wells GA et al. Biologics for rheumatoid arthritis: an overview of Cochrane reviews. Cochrane Database Syst Rev 2009; (4):CD007848.
125. Singh JA, Wells GA, Christensen R et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview. Cochrane Database Syst Rev 2011; (2):CD008794.
126. Stone M, Salonen D, Lax M, et al. Clinical and imaging correlates of response to treatment with infliximab in patients with ankylosing spondylitis, Journal of Rheumatology 2001; 28: 7; 1605-1614.
127. Su Chinyu, Salzberg Bruce A, et al. Efficacy of anti-tumor necrosis factor therapy in patients with ulcerative colitis, The American Journal of Gastroenterology, October 2002, Vol. 97, No. 10, pp. 2577-2584.
128. Sullivan TP, Welsh E, et al. Infliximab for hidradenitis suppurativa. British Journal of Dermatology 2003; 149: 1046-1049.
129. Takeuchi T, Miyasaka N, Inoue K et al. Impact of trough serum level on radiographic and clinical response to infliximab plus methotrexate in patients with rheumatoid arthritis: results from the RISING study. Modern rheumatology / the Japan Rheumatism Association 2009; 19(5):478-87.
130. Takeuchi T, Miyasaka N, Tatsuki Y et al. Baseline tumour necrosis factor alpha levels predict the necessity for dose escalation of infliximab therapy in patients with rheumatoid arthritis. Annals of the rheumatic diseases 2011; 70(7):1208-15.
131. Thorlund K, Druyts E, Avina-Zubieta JA et al. Anti-tumor necrosis factor (TNF) drugs for the treatment of psoriatic arthritis: an indirect comparison meta-analysis. Biologics 2012; 6:417-27.
132. Turkstra E, Ng SK, Scuffham PA. A mixed treatment comparison of the short-term efficacy of biologic disease modifying anti-rheumatic drugs in established rheumatoid arthritis. Current medical research and opinion 2011; 27(10):1885-97.
133. Turner D, Griffiths AM. Acute severe ulcerative colitis in children: a systematic review. Inflamm Bowel Dis 2011; 17(1):440-9.
134. Turner D, Mack D, Leleiko N et al. Severe pediatric ulcerative colitis: a prospective multicenter study of outcomes and predictors of response. Gastroenterology 2010; 138(7):2282-91.
135. Turner D, Mack D, Leleiko N, et al. Severe pediatric ulcerative colitis: a prospective multicenter study of outcomes and predictors of response. Gastroenterology. 2010; 138:2282-2291.
136. Tynjala P, Vahasalo P, Tarkiainen M et al. Aggressive combination drug therapy in very early polyarticular juvenile idiopathic arthritis (ACUTE-JIA): a multicentre randomised open-label clinical trial. Annals of the rheumatic diseases 2011; 70(9):1605-12.
137. United States Food and Drug Administration (FDA). Actemra® (tocilizumab) Prescribing Information. www.fda.gov.
138. United States Food and Drug Administration (FDA). GI Advisory Committee Meeting. 2011. Available online at: www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/GastrointestinalDrugsAdvisoryCommittee/UCM263459.pdf. Last accessed November 22, 2011.
139. US Food and Drug Administration (FDA). Remicade (infliximab). Prescribing Information-March 2013 Update. Available online at:

http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/103772s5345lbl.pdf. Last accessed September 2013.
140. United States Food and Drug Administration (FDA). SIMPONI® ARIA™ (golimumab) Prescribing Information: www.fda.gov. Last accessed July 2013.
141. United States Food and Drug Administration (FDA). Stelara™ (ustekinumab) Prescribing Information. www.fda.gov. Last accessed September 2013.
142. Uppal SS, Hayat SJ, Raghupathy R. Efficacy and safety of infliximab in active SLE: a pilot study. Lupus 2009; 18(8):690-7.
143. van den Bosch F, Kruithof E, et al. Effects of a loading dose regimen of three infusions of chimeric monoclonal antibody to tumour necrosis factor α (infliximab) in spondyloarthropathy: an open pilot study, Ann Rheum Disease 2000; 59: 428-433.
144. van den Bosch F, Kruithof E, et al. Randomized double-blind comparison of chimeric monoclonal antibody to tumor necrosis factor α (infliximab) versus placebo in active spondyloarthropathy, Arthritis and Rheumatism 2002; 48: 3.
145. van der Bijl AE, Teng YK, van Oosterhout M et al. Efficacy of intraarticular infliximab in patients with chronic or recurrent gonarthritis: a clinical randomized trial. Arthritis Rheum 2009; 61(7):974-8.
146. van Rappard DC, Limpens J, Mekkes JR. The off-label treatment of severe hidradenitis suppurativa with TNF-alpha inhibitors: a systematic review. J Dermatolog Treat 2013; 24(5):392-404.
147. van Vollenhoven RF, Geborek P, Forslind K et al. Conventional combination treatment versus biological treatment in methotrexate-refractory early rheumatoid arthritis: 2 year follow-up of the randomised, non-blinded, parallel-group Swefot trial. Lancet 2012; 379(9827):1712-20.
148. Visvanathan S, Rahman MU, Hoffman GS et al. Tissue and serum markers of inflammation during the follow-up of patients with giant-cell arteritis--a prospective longitudinal study. Rheumatology (Oxford) 2011; 50(11):2061-70.
149. Wallace CA, Ruperto N, Giannini E et al. Trials organization; Pediatric Rheumatology Collaborative Study Group; preliminary criteria for clinical remission for select categories of juvenile idiopathic arthritis. J Rheumatol 2004; 31:2290-4.
150. Wells AU. Infliximab in extrapulmonary sarcoidosis: tantalising but inconclusive. Eur Respir J 2008; 31(6):1148-9.
151. Wong AK, Kerkoutian S, Said J et al. Risk of lymphoma in patients receiving antitumor necrosis factor therapy: a meta-analysis of published randomized controlled studies. Clin Rheumatol 2012; 31(4):631-6.
152. Wu Jennifer and Schiff Karin Rashcovsky. Sarcoidosis, American Family Physician, July 2004, Vol. 70, No. 2.
153. Yang Z, Wu Q, Wang F et al. Meta-analysis: effect of preoperative infliximab use on early postoperative complications in patients with ulcerative colitis undergoing abdominal surgery. Aliment Pharmacol Ther 2012; 36(10):922-8.
154. Yee Arthur MF and Pochapin Mark B. Treatment of complicated sarcoidosis with infliximab anti-tumor necrosis factor-α therapy, Ann Intern Med 2001; 135: 27-31.
155. Yoshida K, Fukunaga K, Ikeuchi H et al. Scheduled infliximab monotherapy to prevent recurrence of Crohn's disease following ileocolic or ileal resection: a 3-year prospective randomized open trial. Inflamm Bowel Dis 2012; 18(9):1617-23.

Policy History:

Medical Policy Group, June 2002 **(1)**
Medical Review Committee, June 2002
Medical Policy Administration Committee, August 2002
Available for comment August 26-October 9, 2002
Available for comment December 18, 2002-February 3, 2003
Available for comment February 19-April 7, 2003
Medical Policy Group, February 2004
Available for comment February 27-April 12, 2004
Medical Policy Group, June 2004
Medical Policy Administration Committee, June 2004
Available for comment June 28-August 11, 2004
Medical Policy Administration Committee, August 2004
Available for comment August 12-September 25, 2004
Medical Policy Group, July 2005
Medical Policy Group, March 2006 **(1)**
Medical Policy Administration Committee, March 2006
Available for comment March 25-May 8, 2006
Medical Policy Group, June 2006 **(1)**
Medical Policy Administration Committee, June 2006
Available for comment July 5-August 18, 2006
Medical Policy Group, October 2006 **(1)**
Medical Policy Administration Committee, October 2006
Available for comment October 21-December 4, 2006
Medical Policy Group, March 2007 **(1)**
Medical Policy Administration Committee, March 2007
Available for comment March 23-May 7, 2007
Medical Policy Group, April 2008 **(1)**
Medical Policy Administration Committee, May 2008
Available for comment May 3-June 16, 2008
Medical Policy Group, November 2008 **(1)**
Medical Policy Administration Committee, December 2008
Available for comment December 9, 2008-January 22, 2009
Medical Policy Group, February 2009 **(2)**
Medical Policy Administration Committee, March 2009
Available for comment February 27-April 13, 2009
Medical Policy Group, August 2009 **(1)**
Medical Policy Administration Committee, August 2009
Available for comment August 21-October 5, 2009
Medical Policy Group, October 2009 **(1)**
Medical Policy Administration Committee, October 2009
Available for comment October 20-December 3, 2009
Medical Policy Group, January 2010 **(1)**
Medical Policy Administration Committee, January 2010
Available for comment January 26-March 11, 2010

Medical Policy Group, April 2010 **(1)**: Added coverage for hidradenitis suppurativa
Medical Policy Administration Committee, April 2010
Available for comment April 15-May 29, 2010
Medical Policy Group, November 2010 **(1):** Coding update added J3262 for Actemra (tocilizumab) and J3357 for Stelara (ustekinumab)
Medical Policy Group, April 2011 **(1):** Update to Policy, Key Points, Key Words, Approved by Governing Bodies and References for Actemra treatment for systemic juvenile idiopathic arthritis (SJIA); entire policy reformatted
Medical Policy Administration Committee, May 2011
Available for comment May 25 – July 11, 2011
Medical Policy Group, July 2011 **(3)**: Updated Policy section, Key Points and References
Medical Policy Administration Committee, July 2011
Available for comment July 21 through September 5, 2011
Medical Policy Group, September 2011 **(1):** Updated Approved by Governing Bodies section for FDA approval of Remicade (infliximab) for ulcerative colitis in children >6years old.
Medical Policy Group, March 2012 **(3)**: 2011 Updates-Key Points and References
Medical Policy Group, October 2012 **(3)**: Added coverage for Remicade for JIA and Uveitis, and Actemra for new FDA indication for RA after failed DMARDS. Updated References.
Medical Policy Administration Committee, October 2012
Available for comment October 24 through December 10, 2012
Medical Policy Panel September 2012
Medical Policy Group, May 2013 **(1):** Update to Key Points and References; no change to policy statement
Medical Policy Group, September 2013 **(1)**: Update to Description, Policy, Key Points, Key Words, Governing Bodies, and References to add coverage criteria for SIMPONI ARIA for moderate to severe active rheumatoid arthritis along with its FDA approval, coverage criteria for Stelara for moderate to severe psoriatic arthritis with its FDA approval and coverage criteria for Cimzia for active psoriatic arthritis with its FDA approval
Medical Policy Administration Committee, October 2013
Medical Policy Group, October 2013 **(1)**: Removed ICD-9 Diagnosis codes; no change to policy statement.
Medical Policy Group, October 2013 **(1):** Update to Policy, Key Points, Key Words, Governing Bodies and References to add coverage criteria for Cimzia for active ankylosing spondylitis; update to Key Points and References related to Infliximab
Medical Policy Administration Committee, November 2013
Available for comment October 1 through November 14, 2013
Medical Policy Group, January 2014 **(1):** Coding update 2014: new HCPCS codes, J0717 and J1602 added to coding section, effective 01/01/2014; deleted code J0718 moved to previous coding section effective 12/31/2013