Clinical Policy Bulletin: Certolizumab Pegol (Cimzia)

Number: 0761

Policy

I. Aetna considers certolizumab pegol (Cimzia) (see note) medically necessary for adult members 18 years of age or older with moderately-to-severely active Crohn’s disease as manifested by any of the following signs/symptoms:

   A. Abdominal pain;
   B. Bleeding;
   C. Diarrhea;
   D. Internal fistulae;
   E. Intestinal obstruction;
   F. Megacolon;
   G. Perianal disease;
   H. Weight loss;
   I. Extra-intestinal manifestations: arthritis or spondylitis; and

Crohn’s disease has remained active despite treatment with one of the following:

   A. 6-mercaptopurine/azathioprine; or
   B. Corticosteroids.

II. Aetna considers certolizumab pegol (see Note), alone or in combination with methotrexate, medically necessary for the treatment of adult members 18 years of age or older with moderately-to-severely active rheumatoid arthritis.

III. Aetna considers certolizumab pegol (see Note) medically necessary for persons with active psoriatic arthritis who meet criteria in CPB 0658 - Psoriasis and Psoriatic Arthritis: Biological Therapies.

IV. Aetna considers certolizumab pegol (see Note) medically necessary for reducing signs and symptoms of members with active ankylosing spondylitis who have an inadequate response to 2 or more NSAIDs.
V. Aetna considers certolizumab pegol experimental and investigational for all other indications (e.g., Behcet's disease, ocular inflammation/uveitis, and sarcoidosis; not an all-inclusive list) because its effectiveness for indications other than the ones listed above has not been established.

Note: There are several brands of targeted immune modulators on the market. There is a lack of reliable evidence that any one brand of targeted immune modulator is superior to other brands for medically necessary indications. Enbrel (etanercept), Humira (adalimumab), Remicade (infliximab), Simponi Aria (golimumab intravenous), and Stelara (ustekinumab) brands of targeted immune modulators ("least cost brands of targeted immune modulators") are less costly to Aetna. Consequently, because other brands (e.g., Actemra (tocilizumab), Cimzia (certolizumab), Cosentyx (secukinumab), Entvyio (vedolizumab), Kineret (anakinra), Orencia (abatacept), Otezla (apremilast), Rituxan (rituximab), Simponi (golimumab) and Xeljanz (tofacitinib)) of injectables are more costly than these least cost brands of targeted immune modulators, and least cost brands of targeted immune modulators are at least as likely to produce equivalent therapeutic results, no other brands of targeted immune modulator will be considered medically necessary unless the member has a contraindication, intolerance or incomplete response to at least 2 of the least cost brands of targeted immune modulator: Enbrel, Humira, Remicade, Simponi Aria, or Stelara, for the same medically necessary indication. If the least costly targeted immune modulator does not have the labeled indication (see appendix), then Aetna considers medically necessary another brand of targeted immune modulator that has the required labeling indication.

See also: CPB 0314 - Rituximab (Rituxan); CPB 0315 - Enbrel (Etanercept); CPB 0341 - Remicade (Infliximab); CPB 0595 - Kineret (Anakinra); CPB 0655 - Adalimumab (Humira); and CPB 0720 - Abatacept (Orencia).

Background

Crohn's disease is a chronic, inflammatory bowel disease that affects more than 1 million people worldwide. It has no cure and its cause is unknown. Crohn's disease can cause diarrhea, fever, rectal bleeding, and malnutrition, narrowing of the intestinal tract, obstructions, abscesses, cramping, and abdominal pain. It also can lead to fistulas (abnormal connections) leading from the intestine to the skin or internal organs.

Certolizumab pegol (Cimzia) (UCB, Inc., Smyrna, GA) is the first pegylated anti-tumor necrosis factor (TNF)-alpha monoclonal antibody that has a high-affinity for human TNF-alpha and selectively targets TNF-alpha in inflamed tissue. Excess TNF-alpha production has been implicated in a wide variety of diseases, including Crohn's disease, rheumatoid arthritis (RA) and other autoimmune diseases.

In April 2008, the U.S. Food and Drug Administration (FDA) approved certolizumab pegol for adults with moderately-to-severely active Crohn's disease who have not responded to conventional therapies. The approval of certolizumab pegol was based on safety and efficacy data from clinical trials in more than 1,500 patients with Crohn's disease.
The Pegylated Antibody Fragment Evaluation in Crohn's Disease: Safety and Efficacy (PRECiSE) program enrolled more than 1,300 patients in 4 trials and evaluated the safety and efficacy of certolizumab pegol. The PRECiSE 1 and PRECiSE 2 studies were 26-week trials that evaluated induction and short-term maintenance of remission. Outcome data from the PRECiSE 3 and PRECiSE 4 studies, designed to evaluate long-term maintenance of remission, have not yet been published.

The PRECiSE 1 trial, a placebo-controlled phase III study, stratified patients (n = 662) according to baseline levels of C-reactive protein (CRP). Patients were randomly assigned to receive either 400 mg of certolizumab pegol or placebo subcutaneously at weeks 0, 2, and 4 and then every 4 weeks. Primary endpoints were the induction of a response at week 6 and a response at both weeks 6 and 26. Among patients with a baseline CRP level of at least 10 mg per liter, 37 % of patients in the certolizumab group had a response at week 6, as compared with 26 % in the placebo group. At both weeks 6 and 26, the corresponding values were 22 % and 12 %, respectively. In the overall population, response rates at week 6 were 35 % in the certolizumab group and 27 % in the placebo group; at both weeks 6 and 26, the response rates were 23 % and 16 %, respectively. At weeks 6 and 26, the rates of remission in the 2 groups did not differ significantly. Serious adverse events were reported in 10 % of patients in the certolizumab group and 7 % of those in the placebo group; serious infections were reported in 2 % and less than 1 %, respectively. In the certolizumab group, antibodies to the drug developed in 8 % of patients, and anti-nuclear antibodies developed in 2 %. The authors concluded that in patients with moderate-to-severe Crohn's disease, induction and maintenance therapy with certolizumab pegol was associated with a modest improvement in response rates, as compared with placebo, but with no significant improvement in remission rates (Sandborn et al, 2007).

The PRECiSE 2 trial, a placebo-controlled study, evaluated the efficacy of certolizumab pegol maintenance therapy in adults (n = 668) with moderate-to-severe Crohn's disease. Certolizumab pegol (400 mg) was administered subcutaneously at weeks 0, 2, and 4 as induction therapy. Patients with a clinical response (defined as reduction of at least 100 from the baseline score on the Crohn's Disease Activity Index [CDAI]) at week 6 were stratified according to their baseline CRP level and were randomly assigned to receive 400 mg of certolizumab pegol or placebo every 4 weeks through week 24, with follow-up through week 26. Among patients with a response to induction therapy at week 6 (n = 428 or 64 %), the response was maintained through week 26 in 62 % of patients with a baseline CRP level of at least 10 mg per liter (the primary endpoint) who were receiving certolizumab pegol (versus 34 % of those receiving placebo) and in 63 % of patients in the intention-to-treat population who were receiving certolizumab pegol (versus 36 % receiving placebo). Among patients with a response to induction therapy at week 6, remission (defined by a CDAI score of 150) at week 26 was achieved in 48 % of patients in the certolizumab group and 29 % of those in the placebo group. The use of immunosuppressants, corticosteroids, and previous treatment with infliximab were not demonstrated to affect the response rate. Serious infections, including one case of pulmonary tuberculosis, occurred in 3 % of patients receiving certolizumab pegol and in less than 1 % of patients receiving placebo. Anti-nuclear antibodies developed in 8 % of the patients in the certolizumab group; antibodies against certolizumab pegol developed in 9 % of all patients who entered the induction phase. The authors concluded that patients with moderate-to-severe Crohn's disease who had a response to induction therapy with 400 mg of certolizumab...
pegol were more likely to have a maintained response and a remission at 26 weeks with continued certolizumab pegol treatment than with a switch to placebo.

A Cochrane systematic review (2008) evaluated the evidence of the effectiveness of TNF-alpha blocking agents in the maintenance of remission in patients with Crohn's disease. Randomized controlled trials involving patients greater than 18 years of age with Crohn's disease who had a clinical response or clinical remission with a TNF-alpha blocking agent, or patients with Crohn's disease in remission but unable to wean from corticosteroids, who were then randomized to maintenance of remission with a TNF-alpha blocking agent or placebo were selected for review. Nine studies met all inclusion criteria. Four different anti-TNF-alpha agents were evaluated (infliximab in 3 studies, CDP571 in 3 studies, adalimumab in 2 studies, and certolizumab in 1 study). The authors reported that infliximab, adalimumab, and certolizumab maintained clinical remission, clinical response, had corticosteroid-sparing effects, and maintained fistula healing in patients with Crohn's disease. There was no evidence to support the use of CDP571 for the maintenance of remission in Crohn's disease. No comparative trials have evaluated the relative efficacy of these agents. Adverse events were similar in the infliximab, adalimumab, and certolizumab groups compared with placebo, but study size and duration generally were insufficient to allow an adequate assessment of serious adverse events associated with long-term use.

In the Crohn's Disease Study Group, Rutgeerts et al (2008) reported the health-related quality of life (HRQoL) of patients with moderately-to-severely active Crohn's disease (n = 292) who received subcutaneous certolizumab pegol. Patients with moderately-to-severely active Crohn's disease (n = 292) received subcutaneous certolizumab pegol 100, 200, or 400 mg or placebo at weeks 0, 4, and 8. A post hoc analysis of the intent-to-treat population (290 patients with HRQoL data) assessed HRQoL by evaluating patients' responses to the self-administered inflammatory bowel disease questionnaire (IBDQ) at baseline and weeks 2, 4, 6, 8, 10, and 12. Patients receiving certolizumab pegol 400 mg at weeks 0, 4, and 8 demonstrated, via their IBDQ total score, significantly greater improvement in HRQoL from baseline to week 12 and at all other time points compared with placebo. In addition, HRQoL improved over time in all certolizumab pegol groups, irrespective of baseline CRP levels. Emotional well-being improved throughout the study for patients receiving certolizumab pegol 400 mg. This improvement was significantly greater than for patients receiving placebo at all time points. In addition, systemic symptoms improved more in patients receiving certolizumab pegol 400 mg than in those receiving placebo at weeks 4, 8, 10, and 12 and approached statistical significance at week 2. The authors concluded that certolizumab pegol 400 mg improved health-related quality of life in patients with moderate-to-severe Crohn's disease.

The prescribing label for certolizumab pegol for Crohn's disease states that 400 mg of certolizumab pegol is administered as a subcutaneous injection initially and at weeks 2 and 4. If a response occurs, 400 mg of certolizumab pegol should be given once every 4 weeks. The most common side effects of certolizumab pegol are headache, upper respiratory infections, abdominal pain, injection site reactions and nausea.

Certolizumab pegol was approved by the FDA on April 24, 2009 for adults with moderately-to-severely active RA. It can be administered as combination therapy with methotrexate (MTX) or as monotherapy. The recommended dose for patients with moderately-to-severely active RA is 400 mg initially and at weeks 2 and 4, followed by
200 mg every other week. For maintenance dosing, 400 mg every 4 weeks can be considered. It is self-administered by subcutaneous injection. According to the prescribing information, certolizumab pegol should not be used in combination with biological disease-modifying antirheumatic drugs (DMARDs) or other TNF blocker therapies.

The FDA approval of Cimzia for RA was based on data from 4 multi-center placebo-controlled phase III trials, involving more than 2,300 patients aged 18 years or older with moderately-to-severely active RA. Patients who received certolizumab pegol together with MTX, experienced a significant reduction in the signs and symptoms of RA at week 24 with some showing clinical responses within 1 to 2 weeks, compared with MTX alone. Additionally, radiographic data showed certolizumab pegol, together with MTX, inhibited progression of joint damage, with a significantly smaller change from baseline in modified Total Sharp Score (TSS) at 24 and 52 weeks of treatment, compared with MTX alone (p < 0.001).

A review of the evidence for targeted immunomodulators by the Drug Effectiveness Review Project (DERP) (Thaler, et al., 2012) identified no head-to-head trials providing direct evidence on the comparative efficacy of targeted immune modulators for Crohn’s disease. The review found that the general efficacy of certolizumab pegol, adalimumab, infliximab, and natalizumab for the treatment of moderate to severe Crohn’s disease was supported by several good to fair randomized controlled trials and meta-analyses including 6901 patients. In efficacy trials 26% to 57% of patients treated with targeted immune modulators achieved a Crohn’s Disease Activity Index remission (CDAI <150), compared with 12% to 30% of patients on placebo.

The DERP review (Thaler, et al., 2012) found good to fair evidence from meta-analyses and large randomized controlled trials that certolizumab pegol, abatacept, adalimumab, anakinra, etanercept, golimumab, infliximab, rituximab, and tocilizumab are statistically significantly more efficacious than placebo for the treatment of rheumatoid arthritis. The review stated that data were too heterogeneous to conduct indirect comparisons of certolizumab pegol with other targeted immune modulators for rheumatoid arthritis.

Keystone et al (2008) evaluated the safety and effectiveness of 2 dosage regimens of certolizumab pegol as adjunctive therapy to MTX in patients with active RA who had an inadequate response to MTX therapy alone. In this 52-week, phase III, multi-center, randomized, double-blind, placebo-controlled, parallel-group trial, 982 patients were randomized 2:2:1 to receive treatment with 400 mg of certolizumab pegol as an initial dosage and at weeks 2 and 4, with a subsequent dosage of 200 mg or 400 mg given every 2 weeks, plus MTX, or placebo plus MTX. Co-primary endpoints were the response rate at week 24 according to the American College of Rheumatology 20 % criteria for improvement (ACR20) and the mean change from baseline in the modified TSS at week 52. At week 24, ACR20 response rates using non-responder imputation for the certolizumab pegol 200-mg and 400-mg groups were 58.8 % and 60.8 %, respectively, as compared with 13.6 % for the placebo group. Differences in ACR20 response rates versus placebo were significant at week 1 and were sustained to week 52 (p < 0.001). At week 52, mean radiographic progression from baseline was reduced in patients treated with 200 mg of certolizumab pegol (0.4 Sharp units) or 400 mg (0.2 Sharp units) as compared with that in placebo-treated patients (2.8 Sharp units) (p < 0.001 by rank analysis). Improvements in all ACR core set of disease
activity measures, including physical function, were observed by week 1 with both
certolizumab pegol dosage regimens. Most adverse events were mild or moderate.
The authors concluded that 200 mg or 400 mg of certolizumab pegol plus MTX
resulted in a rapid and sustained reduction in RA signs and symptoms, inhibited the
progression of structural joint damage, and improved physical function as compared
with placebo plus MTX treatment in RA patients with an incomplete response to MTX.

Smolen et al (2009) reported the safety and efficacy of certolizumab pegol plus MTX in
a randomized controlled trial (RAPID 2 study). Patients (n = 619) were randomized
2:2:1 to 400 mg of certolizumab pegol at weeks 0, 2 and 4 followed by 200 mg or 400
mg of certolizumab pegol plus MTX, or placebo plus MTX, every 2 weeks for 24
weeks. The primary endpoint was ACR20 response at week 24. Secondary endpoints
included ACR50 and ACR70 responses, change from baseline in modified TSS Score,
ACR core set variables and physical function. The authors reported that significantly
more patients in the 200 mg and 400 mg certolizumab pegol groups achieved an
ACR20 response versus placebo (p < or = 0.001); rates were 57.3 %, 57.6 % and 8.7
%, respectively. Certolizumab pegol significantly inhibited radiographic progression;
mean changes from baseline in modified TSS at week 24 were 0.2 and -0.4,
respectively, versus 1.2 for placebo (rank analysis p < or = 0.01). Certolizumab pegol-
treated patients reported rapid and significant improvements in physical function
versus placebo; mean changes from baseline in the Disability Index of the Health
Assessment Questionnaire (HAQ DI) at week 24 were -0.50 and -0.50, respectively,
versus -0.14 for placebo (p < or = 0.001). Most adverse events were mild or moderate,
with low incidence of withdrawals due to adverse events. Five patients developed
tuberculosis. The authors concluded that certolizumab pegol plus MTX were more
efficacious than placebo plus MTX.

Fleischmann et al (2009) evaluated the safety and efficacy of certolizumab pegol in a
randomized, double-blind, placebo-controlled study (FAST4WARD study) in RA
patients (n = 220) previously failing one or more DMARDs. Patients were randomized
1:1 to receive 400 mg of subcutaneous certolizumab pegol (n = 111) or placebo (n =
109) every 4 weeks. The primary endpoint was the ACR20 response at week 24.
Secondary endpoints included ACR50/70 response, ACR component scores, 28-joint
Disease Activity Score Erythrocyte Sedimentation Rate 3 (DAS28(ESR)3), patient-
reported outcomes (including physical function, HRQoL, pain and fatigue) and safety.
At week 24, the ACR20 response rates were 45.5 % for 400 mg of certolizumab pegol
every 4 weeks versus 9.3 % for placebo (p < 0.001). Differences for certolizumab
pegol versus placebo in the ACR20 response were statistically significant as early as
week 1 through week 24 (p < 0.001). Significant improvements in ACR50, ACR
components, DAS28(ESR)3 and all patient-reported outcomes were also observed
early with certolizumab pegol and were sustained throughout the study. Most adverse
events were mild or moderate and no deaths or cases of tuberculosis were reported.
The authors concluded that 400 mg of certolizumab pegol monotherapy every 4 weeks
effectively reduced the signs and symptoms of active RA in patients previously failing
one or more DMARDs compared with placebo, and demonstrated an acceptable safety
profile.

A black box warning is included in the certolizumab pegol label. The warning states
that patients taking certolizumab pegol are at increased risk for serious infections that
may lead to hospitalizations and death. Most patients who developed these infections
were taking concomitant immunosuppressants such as MTX or corticosteroids.
Tuberculosis (frequently disseminated or extra-pulmonary at clinical presentation), invasive fungal infections, and other opportunistic infections, have been observed in patients receiving certolizumab pegol. Some of these infections have been fatal. The labeling states that Cimzia should be discontinued if a patient develops a serious infection or sepsis.

Anti-tuberculosis treatment of patients with latent tuberculosis infection reduces the risk of reactivation in patients receiving treatment with TNF blockers; however, active tuberculosis has developed in patients receiving certolizumab pegol whose tuberculin test was negative. Patients should be evaluated for tuberculosis risk factors and tested for latent tuberculosis infection prior to initiating certolizumab pegol and during therapy. Treatment of latent tuberculosis infection should be initiated prior to therapy with certolizumab pegol. In addition, patients should be monitored for signs and symptoms of active tuberculosis, including patients who tested negative for latent tuberculosis infection.

The labeling states that patients taking Cimzia are at increased risk of bacterial, viral and other opportunistic infections. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with Cimzia. The labeling states that the risk and benefits of treatment with Cimzia should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

According to the product labeling, patients taking Cimzia are at increased risk of invasive fungal infections, including histoplasmosis, coccidiodomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. The labeling states that empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness.

A black box warning states that cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF blockers. Cimzia has not been formally studied in patients with CHF; however, in clinical studies in CHF of another TNF blocker, a higher rate of serious CHF-related adverse reactions was observed. The labeling recommends that caution be exercised when using Cimzia in patients who have heart failure, and that patients be carefully monitored.

Rozenblit and Lebwohl (2009) stated that the prevalence of psoriasis is estimated to be 2.2 % in the United States, and 6 to 39 % of patients with psoriasis also develop psoriatic arthritis. New advances have been made in developing treatment options. A new human TNF-alpha antibody, golimumab, has been shown to significantly improve symptoms of psoriatic arthritis. In addition, clinical trials of certolizumab pegol show promising results for treating rheumatoid arthritis and suggest that it may be applicable for treating psoriasis and psoriatic arthritis in the future. New biological therapies also include antibodies to interleukin-12 and interleukin-23. Phase II studies suggest that ustekinumab is effective in alleviating symptoms of psoriasis and psoriatic arthritis. However, longer studies with radiographical evaluation will be required before their impact on joint destruction can be assessed. In a review on the treatment of peripheral arthritis in psoriatic arthritis, Soriano and Rosa (2009) noted that among new drugs, evidence of efficacy has already been published with regard to golimumab and
ustekinumab; results are forthcoming from trials with abatacept, certolizumab pegol, and rituximab. Furthermore, Farhi and Dupin (2009) stated that new biological therapies under investigation in the treatment of psoriasis include certolizumab, golimumab, and ustekinumab.

Certolizumab has been approved by the FDA for use in adults with active psoriatic arthritis (UCB, 2013). FDA approval of Cimzia for active psoriatic arthritis was based on data from the RAPIDTM-PsA study, an ongoing, phase 3, multicenter, randomized, double-blind, placebo-controlled trial designed to evaluate the efficacy and safety of certolizumab pegol in 409 patients with active and progressive adult onset psoriatic arthritis. Patients received a loading dose of certolizumab 400 mg at weeks 0, 2 and 4 or placebo, followed by either certolizumab 200 mg every other week, certolizumab 400 mg every 4 weeks, or placebo every other week. Patients were evaluated for signs and symptoms of psoriatic arthritis using the ACR20 response at week 12 and for structural damage using the modified Total Sharp Score (mTSS) at week 24.

ACR20, 50, and 70 response rates at weeks 12 and 24 were higher for each certolizumab dose group relative to placebo (UCB, 2013). Patients treated with certolizumab 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. Patients treated with certolizumab 400 mg every four weeks did not demonstrate greater inhibition of radiographic progression at week 24, compared with placebo-treated patients. Treatment with certolizumab also resulted in improvement in skin manifestations in patients with psoriatic arthritis. However, the safety and efficacy of certolizumab in the treatment of patients with plaque psoriasis has not been established.

Adverse events occurred in 62% of patients in the certolizumab group (combined dose) compared to 68% of patients in the placebo group (UCB, 2013). Serious adverse events occurred in 7% of patients in the certolizumab group (combined dose) compared to 4% of patients in the placebo group. According to the manufacturer, the safety profile for patients with psoriatic arthritis treated with certolizumab was similar to the safety profile seen in patients with rheumatoid arthritis and in patients with previous experience with certolizumab.

Recommended dosing of certolizumab pegol for psoriatic arthritis is 400 mg initially and at week 2 and 4, followed by 200 mg every other week; for maintenance dosing, 400 mg every 4 weeks can be considered.

Machado et al (2013) noted that biological agents directed against TNF represent therapeutic options for patients with ankylosing spondylitis with high disease activity despite use of non-steroidal anti-inflammatory drugs. To evaluate the safety and effectiveness of the anti-TNF agents adalimumab, certolizumab, etanercept, golimumab, and infliximab for the treatment of ankylosing spondylitis, these researchers performed a systematic review of randomized clinical trials on adult patients with ankylosing spondylitis using articles culled from the Embase, Medline, Cochrane Controlled Trials Register and LILACS databases (September 2012), manual literature search, and the gray literature. Study selections and data collection were performed by 2 independent reviewers, with disagreements solved by a 3rd reviewer. The following outcomes were evaluated: ASAS 20 response, disease activity, physical function, vertebral mobility, adverse events, and withdraws. The meta-analysis was performed using the Review Manager 5.1 software by applying the
random effects model. A total of 18 studies were included in this review. No study of certolizumab was included. Patients treated with anti-TNF agents were more likely to display an ASAS 20 response after 12/14 weeks (RR 2.21; 95% confidence interval [CI]: 1.91; to 2.56) and 24 weeks (RR 2.68; 95% CI: 2.06 to 3.48) compared with controls, which was also true for several other efficacy outcomes. Meta-analysis of safety outcomes and withdraws did not indicate statistically significant differences between treatment and control groups after 12 or 30 weeks. The authors concluded that adalimumab, etanercept, golimumab, and infliximab can effectively reduce the signs and symptoms of the axial component of ankylosing spondylitis. Moreover, they stated that safety outcomes deserve further study, especially with respect to long-term follow-ups.

The FDA has approved Cimzia for adults with ankylosing spondylitis (UCB, 2013). The approval of Cimzia for adults with active ankylosing spondylitis was based on a phase 3, multicenter, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of Cimzia in patients with active axial spondyloarthritis, in which the majority had ankylosing spondylitis.

In the efficacy and safety study of certolizumab, patients with active axial spondyloarthritis were randomized (1:1:1) to receive certolizumab 200 mg every two weeks, 400 mg every four weeks or placebo (UCB, 2013). There were a total of 325 patients in the study, of which 178 had ankylosing spondylitis. All patients received a loading dose with certolizumab or placebo at weeks 0, 2 and 4. The primary efficacy variable, the proportion of patients achieving an ASAS20 response rate at week 12, was met with clinical and statistical significance in both dosing arms versus placebo.

A greater proportion of ankylosing spondylitis patients treated with certolizumab 200 mg every two weeks or 400 mg every four weeks achieved ASAS20 response at week 12, compared with ankylosing spondylitis patients treated with placebo (UCB, 2013). Responses were similar in patients receiving certolizumab 200 mg every two weeks and 400 mg every four weeks.

In this study, adverse events occurred in 70.4% of patients in the certolizumab group (combined dose) compared to 62.6% of patients in the placebo group (UCB, 2013). Serious adverse events occurred in 4.7% of patients in both the certolizumab group (combined dose) and in the placebo group. According to the manufacturer, the safety profile for patients with ankylosing spondylitis treated with certolizumab was similar to the safety profile seen in patients with rheumatoid arthritis and in patients with previous experience with certolizumab.

Recommended dosing of certolizumab pegol in ankylosing spondylitis is 400 mg (given as 2 subcutaneous injections of 200 mg each) initially and at weeks 2 and 4, followed by 200 mg every other week or 400 mg every 4 weeks.

Rifkin et al (2013) discussed the differences in the mechanism of action, route of administration, indication, and effectiveness of TNF inhibitors used in the treatment of ocular inflammation. A review of the literature in the PubMed, Medline, and Cochrane databases was conducted to identify clinical trials, comparative studies, case series, and case reports describing the use of tumor necrosis factor inhibitors in uveitis therapy. The search was limited to primary reports published in English with human subjects from 1990 to the present, yielding 5,238 manuscripts. In addition, referenced articles from the initial searches were hand searched to identify additional relevant
reports. After title and abstract selection, duplicate elimination, and manual search, a total of 69 papers were selected for analysis. Exclusion criteria included review articles and case reports on the effectiveness of adalimumab, etanercept, and infliximab. Manuscripts with fewer than 20 study subjects were excluded if other larger studies existed on the use of the same drug for a particular indication. Studies with less than 6 months of patient follow-up were also excluded, except in the case where no other data were available. Articles meeting these criteria were then reviewed by the 3 authors for inclusion in this review. Tumor necrosis factor inhibitors have been shown to decrease inflammation associated with a number of rheumatologic conditions. Three of the 5 commercially available TNF inhibitors – adalimumab, etanercept, and infliximab – have been studied for their effectiveness in treatment of ocular inflammation. Etanercept appears to be inadequate in controlling ocular inflammation and is not recommended for the treatment of uveitis. Adalimumab and infliximab, however, have shown encouraging results in multiple trials. Serious potential side effects such as infection, including re-activation of latent tuberculosis, malignancy, and demyelinating disease, may limit the use of TNF inhibitors in uveitis. Proper screening of patients prior to initiating these therapies may decrease these risks. The authors concluded that early success with adalimumab and infliximab has paved the way for new TNF inhibitors and other corticosteroid-sparing drugs to emerge in the treatment of ocular inflammation. They stated that future studies are on the horizon to determine the long-term safety and effectiveness of newer TNF inhibitors such as certolizumab and golimumab.

Sanchez-Cano et al (2013) stated that TNF-alpha plays a central role in both the inflammatory response and that of the immune system. Thus, its blockade with the so-called anti-TNF agents (infliximab, etanercept, adalimumab, certolizumab pegol, and golimumab) has turned into the most important tool in the management of a variety of disorders, such as rheumatoid arthritis, spondyloarthropathies, inflammatory bowel disease, and psoriasis. Nonetheless, theoretically, some other autoimmune disorders may benefit from these agents. These investigators reviewed these off-label uses of anti-TNF blockers in 3 common conditions: (i) Behcet’s disease, (ii) sarcoidosis, and (iii) non-infectious uveitis. They noted that due to the insufficient number of adequate clinical trials and consequently to their lower prevalence compared to other immune disorders, this review was mainly based on case reports and case series.

Appendix

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<th>Brand Name</th>
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<th>FDA Labeled Indications</th>
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<td>Actemra</td>
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<td>Rheumatoid arthritis</td>
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<td>Systemic juvenile idiopathic arthritis</td>
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<td>Cimzia</td>
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<td>Certolizumab Pegol (Cimzia)</td>
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<td>Juvenile idiopathic arthritis</td>
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<td>Plaque psoriasis</td>
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<td>Psoriatic arthritis</td>
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<td>Crohn's disease</td>
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<td>Psoriatic arthritis</td>
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</table>
Certolizumab Pegol (Cimzia)

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<th>Drug</th>
<th>Treatment</th>
<th>Condition</th>
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<tr>
<td>Rituxan</td>
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<td>golimumab</td>
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<td>ustekinumab</td>
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<td>Xeljanz</td>
<td>tofacitinib</td>
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</table>

**CPT Codes / HCPCS Codes / ICD-9 Codes**

**HCPCS codes covered if selection criteria are met:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>J0717</td>
<td>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)</td>
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</table>

**Other HCPCS codes related to the CPB:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>J0702</td>
<td>Injection, betamethasone acetate and betamethasone sodium phosphate, per 3 mg</td>
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<tr>
<td>J1020</td>
<td>Injection, methylprednisolone acetate, 20 mg</td>
</tr>
<tr>
<td>J1030</td>
<td>Injection, methylprednisolone acetate, 40 mg</td>
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<tr>
<td>J1040</td>
<td>Injection, methylprednisolone acetate, 80 mg</td>
</tr>
<tr>
<td>J1094</td>
<td>Injection, dexamethasone acetate, 1 mg</td>
</tr>
<tr>
<td>J1100</td>
<td>Injection, dexamethasone sodium phosphate, 1mg</td>
</tr>
<tr>
<td>J1700</td>
<td>Injection, hydrocortisone acetate, up to 25 mg (i.e., Hydrocortone acetate)</td>
</tr>
</tbody>
</table>
J1710  Injection, hydrocortisone sodium phosphate, up to 50 mg (i.e., Hydrocortone phosphate)

J1720  Injection, hydrocortisone sodium succinate, up to 100 mg (i.e., Solu-Cortef)

J2650  Injection, prednisolone acetate, up to 1 ml (i.e., Key-Pred 25, Key-Pred 50, Predcor-25, Predcor-50, Predoject 50, Predalone-50, Predicort-50)

J2920  Injection, methylprednisolone sodium succinate, up to 40 mg (i.e., Solu-Medrol)

J2930  Injection, methylprednisolone sodium succinate, up to 125 mg (i.e., Solu-Medrol)

J3301  Injection, triamcinolone acetonide, not otherwise specified, per 10 mg (i.e., Kenalog)

J3302  Injection, triamcinolone diacetate, per 5 mg (i.e., Aristocort)

J3303  Injection, triamcinolone hexacetonide, per 5 mg (i.e., Aristospan)

J7500  Azathioprine, oral, 50 mg

J7501  Azathioprine, parenteral, 100 mg

J7506  Prednisone, oral, per 5 mg

J7509  Methylprednisolone, oral, per 4 mg

J7510  Prednisolone, oral, per 5 mg

J8540  Dexamethasone, oral, 0.25 mg

S0108  Mercaptopurine, oral 50 mg

**ICD-9 codes covered if selection criteria are met:**

555.0 - 555.9  Regional enteritis [adults with moderate to severe Crohn's disease who have not responded to conventional therapies]

696.0  Psoriatic arthropathy [see CPB 658 Psoriasis: Biological Therapies]

714.0 - 714.2  Rheumatoid arthritis

720.0  Ankylosing spondylitis

**ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):**

135  Sarcoidosis

136.1  Behcet's syndrome

364.3  Unspecified iridocyclitis [uveitis NOS]
The above policy is based on the following references:


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