Clinical Policy Bulletin:  
Golimumab (Simponi and Simponi Aria)

Number: 0790

Policy

Note: Simponi Aria (I.V. golimumab) REQUIRES PRECERTIFICATION.*

Aetna considers intravenously administered golimumab (Simponi Aria) medically necessary for the treatment of adult members 18 years of age or older with moderately-to-severely active rheumatoid arthritis when used in combination with methotrexate. Aetna considers I.V. golimumab experimental and investigational for all other indications.

Aetna considers subcutaneously administered golimumab (Simponi) medically necessary for the treatment of adult members 18 years of age or older with any of the following conditions:

- Moderately-to-severely active rheumatoid arthritis when used in combination with methotrexate;  
  or
- Active psoriatic arthritis, for members who meet medical necessity criteria in CPB 0658 - Biological Therapies: Psoriasis and Psoriatic Arthritis; or
- Active ankylosing spondylitis with evidence of inflammatory disease in members who have had an inadequate response to NSAIDS (e.g., celecoxib, diclofenac, ibuprofen, indomethacin, meloxicam, naproxen, sulindac, or valdecoxib) (unless contraindicated); or
- Active ulcerative colitis that meets either of the following criteria:
  - Member is hospitalized with fulminant ulcerative colitis (i.e., persons severe ulcerative colitis who have more than 10 stools per day, continuous bleeding, abdominal pain, and distension, and acute, severe toxic symptoms including fever and anoxia); or
  - Member has moderate to severe active ulcerative colitis and meets all of the following criteria:
    - Member is refractory to or requires continuous immunosuppression with corticosteroids (e.g., methylprednisolone, prednisone) at a dose of prednisone 40 to 60 mg/day (or equivalent) for 30 days for oral therapy or 7 to 10 days for IV therapy); and
    - Member is refractory to or has a contraindication to 5-aminosalicylic acid agents (e.g., balsalazide, mesalamine, sulfasalazine); and

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Member is refractory to or has a contraindication to immunosuppressants (e.g., 6-mercaptopurine or azathioprine).

Aetna considers subcutaneously administered golimumab experimental and investigational for all other indications (e.g., asthma, sarcoidosis) because its effectiveness for indications other than the ones listed above has not been established.

Aetna considers golimumab experimental and investigational for the treatment of ocular inflammatory disorders (e.g., Behcet's disease, panuveitis, posterior uveitis, and scleritis; not an all-inclusive list) because its effectiveness for these indications 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), Entyvio (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.

Note: * Precertification of I.V. golimumab (Simponi Aria) is required of all Aetna participating providers and members in applicable plan designs. For precertification of I.V. golimumab, call (866) 503-0857, or fax (866) 267-3277.

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

Golimumab, a human monoclonal antibody, inhibits the biological activity of tumor necrosis factor alpha (TNF-alpha). Elevated TNF-alpha levels have been implicated in the pathophysiology of several chronic inflammatory diseases, including rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS). Tumor necrosis factor-alpha is an important mediator of the articular inflammation that is characteristic of these diseases.

Golimumab (Simponi) (Centocor Ortho Biotech Inc., Malvern, PA) for subcutaneous use was approved by the U.S. Food and Drug Administration (FDA) on April 24, 2009 for adults with moderately-to-severely active rheumatoid arthritis, active psoriatic arthritis, and active ankylosing spondylitis. It is intended for use in combination with methotrexate (MTX) in patients with rheumatoid arthritis. It also may be used with or without MTX for active psoriatic arthritis and alone in patients with active ankylosing spondylitis, a chronic inflammatory arthritis of the spine. For patients with rheumatoid arthritis, active
psoriatic arthritis, or active ankylosing spondylitis, corticosteroids, non-biologic disease-modifying antirheumatic drugs (DMARDs), and/or non-steroidal anti-inflammatory drugs (NSAIDs) may be continued during treatment with golimumab.

In the clinical studies submitted to the FDA by the manufacturer, patients who received golimumab showed improvements in the signs and symptoms common to their form of arthritis (i.e., RA, active PsA, and active AS).

The safety and effectiveness of golimumab in RA were evaluated in 3 multi-center, randomized, double-blind, controlled trials (studies RA-1, RA-2, and RA-3). Patients (n = 1,542) 18 years of age or older with moderately- to severely active RA diagnosed according to the American College of Rheumatology (ACR) criteria at least 3 months prior to the study, with at least 4 swollen and 4 tender joints were included. Golimumab was administered subcutaneously at doses of 50 mg or 100 mg every 4 weeks. Double-blinded controlled efficacy data were collected and analyzed through week 24. Patients were allowed to continue stable doses of concomitant low-dose corticosteroids (equivalent to 10 mg or less of prednisone/day) and/or NSAIDs and patients may have received oral MTX during the trials. The primary endpoint in study RA-1 and study RA-2 was the percentage of patients achieving an ACR response at week 14 and primary endpoint in study RA-3 was the percentage of patients achieving an ACR 50 response at week 24. In studies RA-1, RA-2, and RA3, the median duration of rheumatoid arthritis disease was 9.4, 5.7, and 1.2 years; and 99 %, 75 %, and 54 % of the patients used at least 1 DMARD in the past, respectively. Approximately 77 % and 57 % of patients received concomitant NSAIDs and low-dose corticosteroids, respectively, in the 3 pooled RA trials. A greater percentage of patients treated with the combination of golimumab and MTX achieved ACR responses at week 14 (studies RA-1 and RA-2) and week 24 (studies RA-1, RA-2, and RA-3) versus patients treated with MTX alone. There was no clear evidence of improved ACR response with the higher golimumab dose group (100 mg) compared to the lower dose group (50 mg). In the subset of patients who received golimumab in combination with MTX (n = 103) in study RA-1, the proportion of patients achieving ACR 20, 50 and 70 responses at week 14 were 40 %, 18 %, and 13 %, respectively, compared with 17 %, 6 %, and 2 %, respectively, in the placebo plus MTX group (n = 107). ACR responses were observed in 38 % of patients treated with the combination of 50-mg golimumab and MTX at the first assessment (week 4) after the initial golimumab administration. In studies RA-1 and RA-2, the 50-mg golimumab groups demonstrated a greater improvement compared to the control groups in the change in mean Health Assessment Questionnaire Disability Index (HAQ-DI) score from baseline to week 24: 0.25 versus 0.05 in RA-1, 0.47 versus 0.13 in RA-2, respectively. Also, in studies RA-1 and RA-2, the 50-mg golimumab groups had a greater proportion of HAQ responders (change from baseline greater than 0.22) compared to the control groups at week 24: 44 % versus 28 %, 65 % versus 35 %, respectively.

The safety and efficacy of golimumab in active PsA were evaluated in a multi-center, randomized, double-blind placebo-controlled trial in 405 adult patients with moderately-to-severely active PsA with at least 3 swollen joints and 3 tender joints despite NSAID or DMARD therapy (study PsA). Patients in this study had a diagnosis of active PsA for at least 6 months with a qualifying psoriatic skin lesion of at least 2 cm in diameter. Previous treatment with a biologic TNF-blocker was not permitted. Patients were randomly assigned to placebo (n = 113), 50-mg golimumab (n = 146), or 100-mg golimumab (n = 146) given subcutaneously every 4 weeks. Patients were allowed to receive stable doses of concomitant MTX (25 mg or less/week), low-dose oral corticosteroids (equivalent to 10 mg or less of prednisone/day), and/or NSAIDs during the trial. The use of other DMARDs including sulfasalazine (SSZ), hydroxychloroquine (HCQ), cytotoxic agents, or other biologics was prohibited. The primary endpoint was the percentage of patients achieving ACR 20 response at week 14. Placebo-controlled efficacy data were collected and analyzed through week 24. Patients with each subtype of active PsA were enrolled, including polyarticular arthritis with no rheumatoid nodules (43 %), asymmetric peripheral
arthritis (30 %), distal inter-phalangeal (DIP) joint arthritis (15 %), spondylitis with peripheral arthritis (11 %), and arthritis mutilans (1 %). The median duration of active psoriatic arthritis disease was 5.1 years, 78 % of patients received at least 1 DMARD in the past, approximately 48 % of patients received MTX, and 16 % received low-dose oral steroids. Golimumab with or without MTX resulted in significant improvement in signs and symptoms compared with placebo with or without MTX as demonstrated by the proportion of patients with an ACR 20 response at week 14. There was no clear evidence of improved ACR response with the higher golimumab dose group (100 mg) compared to the lower dose group (50 mg). ACR responses observed in the golimumab-treated groups were similar with or without concomitant MTX. Similar ACR 20 responses at week 14 were observed in patients with different active PsA subtypes. Treatment with golimumab resulted in improvement in enthesitis and skin manifestations in patients with active PsA. However, the safety and efficacy of golimumab in the treatment of patients with plaque psoriasis has not been established.

The safety and efficacy of golimumab in AS were evaluated in a multi-center, randomized, double-blind placebo-controlled trial. Adult patients (n = 356) with active AS according to modified New York criteria for at least 3 months (study AS) with symptoms of active disease (defined as a Bath AS Disease Activity Index (BASDAI) of 4 or greater and visual analogue scale (VAS) for total back pain of 4 or greater, on a scale of 0 to 10 cm) despite current or previous NSAID therapy. Patients were excluded if they were previously treated with a biologic TNF-blocker or if they had complete ankylosis of the spine. Patients were randomly assigned to placebo (n = 78), 50-mg golimumab (n = 138), or 100-mg golimumab (n = 140) administered subcutaneously every 4 weeks. Patients were allowed to continue stable doses of concomitant MTX, SSZ, HCQ, low dose corticosteroids (equivalent to less than 10 mg of prednisone a day), and/or NSAIDs during the trial. The use of other DMARDs including cytotoxic agents or other biologics was prohibited. The primary endpoint was the percentage of patients achieving an Assessment in Ankylosing Spondylitis (ASAS) 20 response at week 14. Placebo-controlled efficacy data were collected and analyzed through week 24. The median duration of ankylosing spondylitis disease was 5.6 years, median duration of inflammatory back pain was 12 years, 83 % were HLA-B27 positive, 24 % had prior joint surgery or procedure, and 55 % received at least 1 DMARD in the past. During the trial, the use of concomitant DMARDS and/or NSAIDS was: MTX (20 %), SSZ (26 %), HCQ (1 %), low-dose oral steroids (16 %), and NSAIDs (90 %). Golimumab, with or without DMARDs, resulted in a significant improvement in signs and symptoms, compared with placebo, with or without DMARDs, as demonstrated by the proportion of patients with an ASAS 20 response at week 14. There was no clear evidence of improved ASAS response with the higher golimumab dose group (100 mg) compared to the lower dose group (50 mg).

Guidance from the National Institute for Health and Clinical Excellence (NICE, 2011) recommended the use of golimumab in combination with methotrexate as an option for the treatment of rheumatoid arthritis in adults whose rheumatoid arthritis has responded inadequately to conventional DMARDs only, including methotrexate, in persons who have undergone trials of 2 DMARDs, including methotrexate (unless contraindicated). A trial of a DMARD is defined as being normally of 6 months, with 2 months at standard dose, unless significant toxicity has limited the dose or duration of treatment.

Kay et al (2008) assessed the safety, efficacy, and pharmacology of subcutaneous administration of golimumab in patients with active RA despite treatment with MTX. Patients were randomly assigned in a double-blinded manner to receive injections of placebo plus MTX or 50-mg or 100-mg golimumab every 2 or 4 weeks plus MTX through week 48. Patients originally assigned to receive injections every 2 weeks had the interval increased to every 4 weeks starting at week 20. The primary endpoint was the proportion of patients meeting achieving an ACR 20 response at week 16. The study was powered to detect a difference in the primary endpoint when the combined golimumab groups and at least 1 of the individual dose groups were compared with placebo. The primary endpoint was attained. Sixty-one percent of patients in the combined golimumab plus MTX dose groups achieved an ACR 20 response at 02/10/2015
week 16 compared with 37 % of patients in the placebo plus MTX group (p = 0.010). In addition, 79 % of patients in the group receiving 100-mg golimumab every 2 weeks achieved an ACR 20 response (p < 0.001 versus placebo). Through week 20 (after which patients receiving placebo were switched to active infliximab therapy), serious adverse events were reported in 9 % of patients in the combined golimumab groups and in 6 % of patients in the placebo group. The authors concluded that golimumab plus MTX effectively reduces the signs and symptoms of RA and is generally well-tolerated in patients with an inadequate response to MTX.

The phase III Go-Forward study (Keystone et al, 2009) examined the safety and efficacy of golimumab in patients with active RA despite MTX therapy. Patients were randomly assigned in a 3:3:2:2 ratio to receive placebo injections plus MTX capsules (group 1, n = 133), 100-mg golimumab injections plus placebo capsules (group 2, n = 133), 50-mg golimumab injections plus MTX capsules (group 3, n = 89), or 100-mg golimumab injections plus MTX capsules (group 4, n = 89). Injections were administered subcutaneously every 4 weeks. The co-primary endpoints were the proportion of patients achieving an ACR20 response at week 14 and the change from baseline in the HAQ-DI score at week 24. The proportion of patients who achieved an ACR20 response at week 14 was 33.1 % in the placebo plus MTX group, 44.4 % (p = 0.059) in the 100-mg golimumab plus placebo group, 55.1 % (p = 0.001) in the 50-mg golimumab plus MTX group, and 56.2 % (p < 0.001) in the 100-mg golimumab plus MTX group. At week 24, median improvements from baseline in HAQ-DI scores were 0.13, 0.13 (p = 0.240), 0.38 (p < 0.001), and 0.50 (p < 0.001), respectively. During the placebo-controlled portion of the study (through week 16), serious adverse events occurred in 2.3 %, 3.8 %, 5.6 %, and 9.0 % of patients and serious infections occurred in 0.8 %, 0.8 %, 2.2 %, and 5.6 %, respectively. The authors concluded that the addition of golimumab to MTX in patients with active RA despite MTX significantly reduced the signs and symptoms of RA and improved physical function.

Kavanaugh et al (2009) assessed the safety and efficacy of golimumab in adult patients with active PsA who had at least 3 swollen and 3 tender joints and active psoriasis. Patients were randomly assigned to receive subcutaneous injections of placebo (n = 113), 50-mg golimumab (n = 146), or 100-mg golimumab (n = 146) every 4 weeks through week 20. Efficacy assessments through week 24 included ACR20, the Psoriasis Area and Severity Index (PASI) in patients in whom at least 3 % of the body surface area was affected by psoriasis at baseline, the Short Form 36 Health Survey (SF-36), HAQ-DI, the Nail Psoriasis Severity Index (NAPSI), the physician's global assessment of psoriatic nail disease, and enthesitis (using the PsA-modified Maastricht Ankylosing Spondylitis Enthesitis Score [MASES] index). At week 14, 48 % of all patients receiving golimumab, 51 % of patients receiving 50-mg golimumab, and 45 % of patients receiving 100-mg golimumab achieved an ACR20 response (the primary endpoint), compared with 9 % of patients receiving placebo (p < 0.001 for all comparisons). Among the 74 % of patients in whom at least 3 % of the body surface area was affected by psoriasis at baseline, 40 % of those in the 50-mg golimumab group and 58 % of those in the 100-mg golimumab group had at least 75 % improvement in the PASI at week 14 (major secondary endpoint), compared with 3 % of placebo-treated patients (p < 0.001 for both doses). Significant improvement was observed for other major secondary endpoints (the HAQ and the SF-36), the NAPSI, the physician's global assessment of psoriatic nail disease, and the PsA-modified MASES index in each golimumab group compared with placebo. This efficacy was maintained through week 24. Golimumab was generally well-tolerated. The authors concluded that treatment with golimumab at doses of 50-mg and 100-mg significantly improved active PsA and associated skin and nail psoriasis through week 24.

The safety and efficacy of golimumab in active AS were evaluated in the Go-Raise study. Patients with active AS, a BASDAI score of 4 or greater, and a back pain score of 4 or greater were randomly assigned in a 1.8:1.8:1 ratio to receive subcutaneous injections of golimumab (50-mg or 100-mg) or placebo every 4 weeks. The primary endpoint was the proportion of patients with at least 20 % improvement in the ASAS20 criteria at week 14. At randomization, 138, 140, and 78 patients were
assigned to the 50-mg, 100-mg, and placebo groups, respectively. After 14 weeks, 59.4 %, 60.0 %, and 21.8 % of patients, respectively, were ASAS20 responders (p < 0.001). A 40 % improvement in the ASAS criteria at week 24 occurred in 43.5 %, 54.3 %, and 15.4 % of patients, respectively. Patients receiving golimumab also showed significant improvement in the physical and mental component summary scores of the SF-36 Health Survey, the Jenkins Sleep Evaluation Questionnaire score, the BASDAI score, and the Bath AS Functional Index score, but not the Bath AS Metrology Index score. Through week 24, 85.6 % of golimumab-treated patients and 76.6 % of patients in the placebo group had 1 or more adverse event, and 5.4 % and 6.5 % of patients, respectively, had 1 or more serious adverse event. Eight golimumab-treated patients and 1 placebo-treated patient had markedly abnormal liver enzyme values, which were transient. Golimumab was effective and well-tolerated in a large cohort of patients with AS during a 24-week study period (Inman et al, 2008).

In a randomized, double-blind, placebo-controlled study, Wenzel et al (2009) evaluated the safety and effectiveness of golimumab in a large population of patients with uncontrolled, severe persistent asthma. A total of 309 patients with severe and uncontrolled asthma, despite high-dose inhaled corticosteroids and long-acting beta(2) agonists, were randomized 1:1:1:1 to monthly subcutaneous injections of placebo or golimumab (50, 100, or 200 mg) through week 52. Co-primary endpoints were the change from baseline through week 24 in pre-bronchodilator percent-predicted FEV1 and the number of severe asthma exacerbations through week 24. No significant differences were observed for the change in percent-predicted FEV1 (least squares mean: placebo, 2.44 [95 % confidence interval (CI): -0.574 to 5.461]; combined 100-mg and 200-mg, 2.91 [0.696 to 5.116]) or severe exacerbations (mean +/- SD: placebo, 0.5 +/- 1.07 versus combined 100-mg and 200-mg 0.5 +/- 0.97) through week 24. Through week 24, 2.6 % of patients treated with placebo versus 19.5 % of those treated with golimumab discontinued the study agent, and 1.3 % and 7.8 % discontinued study participation, respectively. An unfavorable risk-benefit profile led to early discontinuation of study-agent administration after the week-24 database lock. Through week 76, 20.5 % of patients treated with placebo and 30.3 % of patients treated with golimumab experienced serious adverse events, with serious infections occurring more frequently in golimumab-treated patients. One death and all 8 malignancies occurred in the active groups. The authors concluded that overall, treatment with golimumab did not demonstrate a favorable risk-benefit profile in this study population of patients with severe persistent asthma.

Boyce and colleagues (2010) reviewed the current literature on golimumab (GLM) and provided recommendations for the use of GLM based on the published information. The PubMed, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, International Pharmaceutical Abstracts, and other databases, as well as the Web sites for the ACR and the European Union League Against Rheumatism, were searched for relevant articles published in English between the inception of the databases through April 2010. Pharmacologic, pharmacokinetic, clinical, outcomes, and economic studies as well as meta-analyses, case reports, and select abstracts were eligible for inclusion. Review articles on GLM were not used except to identify other primary papers. A total of 7 clinical studies were identified and used to evaluate the efficacy and tolerability of GLM: 5 in patients with RA (4 subcutaneous administration and 1 intravenous administration), 1 in patients with PsA (subcutaneous), and 1 in patients with AS (subcutaneous). In MTX-naive patients with RA, the number of patients satisfying the ACR20 response criteria (greater than 20 % improvement in ACR response rate) at 24 weeks was significantly higher for the GLM + MTX groups than for the MTX-only groups (62 % versus 49 %, respectively; p < 0.05). In patients with active RA despite MTX therapy, ACR20 responses at 14 to 16 weeks were significantly higher for the combined GLM + MTX groups than for the MTX groups (50 % to 79 % versus 33 % to 37 %, respectively; p < 0.001). Golimumab was more effective than placebo, both with and without MTX, in patients with RA and a history of treatment with 1 or 2 TNF-α inhibitors (ACR20 at 14 weeks, 35 % to 37 % versus 18 %, respectively; p < 0.001). Studies of other TNF-α inhibitors reported ACR20 responses in 53 % to 59 % of patients with active RA at 24 weeks.
Golimumab was also more effective than placebo at 24 weeks in patients with PsA (ACR20, 52 % to 61 % versus 12 %, respectively; p < 0.001) (ASAS40 [40 % improvement based on Assessment in Ankylosing Spondylitis International Working Group criteria], 44 % to 54 % versus 15 %, respectively; p < 0.001). Studies of other TNF-α inhibitors reported ACR20 responses at 24 weeks in 55 % to 57 % of patients with PsA and ASAS40 responses in 46 % to 47 % of patients with AS. The incidence of any adverse effect appeared to be comparable in the GLM (61.2 % to 93.9 %) and placebo groups (59.3 % to 85.3 %), but withdrawals because of adverse effects were higher in the GLM groups (0 % to 12.1 %) than in the placebo groups (0 % to 5.9 %). The incidence of serious infections was comparable for GLM (0 % to 4.4 %) and placebo (0.8 % to 3.5 %). The most frequently reported adverse effects in the GLM groups were injection-site reactions (2.7 % to 37.1 %), nausea (2.7 % to 22.9 %), headache (3.8 % to 21.2 %), nasopharyngitis (1.9 % to 15.0 %), and upper respiratory tract infections (5.7 % to 13.8 %). The authors concluded that based on the results of the studies included in this review, GLM appeared to be more effective than placebo in patients with RA, PsA, or AS. Clinical studies have not directly compared GLM with other TNF-α inhibitors. However, according to the available efficacy and tolerability data, GLM should be considered as the first or second TNF-α inhibitor for the treatment of PsA or AS and as the second or possibly first TNF-α inhibitor in combination with MTX for the treatment of RA.

Bargagli et al (2011) noted that sarcoidosis is a granulomatous lung disease in which several cytokines play a pivotal pathogenetic role. Steroid-resistant disease can be treated with immunosuppressive drugs, anti-malarial therapies and recently with anti-TNF-alpha agents. The use of biological agents for the treatment of sarcoidosis springs from research into the pathogenesis of the disease and also from the experience of rheumatologists with other chronic inflammatory diseases. Rituximab, golimumab and ustekinumab are cytokine modulators, useful in the treatment of immuno-inflammatory disorders, for which randomized trials to evaluate safety and efficacy in sarcoidosis are not yet available. Novel anti-cytokine drugs administered alone or in association may offer a new approach to treatment of the disease.

Sandborn et al (2014) noted that little is known about the efficacy of golimumab for treatment of ulcerative colitis (UC). These investigators evaluated subcutaneous golimumab induction therapy in TNFα-antagonist naive patients with moderate-to-severe UC despite conventional treatment. They integrated double-blind phase 2 dose-finding and phase 3 dose-confirmation trials in a study of 1,064 adults with UC (Mayo score: 6 to 12; endoscopic subscore greater than or equal to 2; 774 patients in phase 3). Patients were randomly assigned to groups given golimumab doses of 100 mg and then 50 mg (phase 2 only), 200 mg and then 100 mg, or 400 mg and then 200 mg, 2 weeks apart. The phase 3 primary endpoint was week-6 clinical response. Secondary endpoints included week-6 clinical remission, mucosal healing, and Inflammatory Bowel Disease Questionnaire (IBDQ) score change. In phase 2, median changes from baseline in the Mayo score were -1.0, -3.0, -2.0, and -3.0, in the groups given placebo, 100 mg/50 mg, 200 mg/100 mg, and 400/200 mg golimumab, respectively. In phase 3, rates of clinical response at week 6 were 51.8 % and 55.0 % among patients given 200 mg/100 mg and 400 mg/200 mg golimumab, respectively, versus 29.7 % among those given placebo (both p < 0.0001). Rates of clinical remission and mucosal healing, and mean changes in IBDQ scores, were significantly greater in both golimumab groups versus the placebo group (p ≤ 0.0005, all comparisons). Rates of serious adverse events were 6.1 % and 3.0 %, and rates of serious infection were 1.8 % and 0.5 %, in the placebo and golimumab groups, respectively. One patient in the 400 mg/200mg group died of surgical complications from an ischio-rectal abscess. The authors concluded that treatment with subcutaneous golimumab induces clinical response, remission, and mucosal healing, and increases quality of life, in larger percentages of patients with active UC than placebo.

On May 15, 2013, the FDA approved Simponi (golimumab) for the treatment of adults with moderate-to-severe ulcerative colitis that is refractory to prior treatment or requires continuous steroid therapy.
The recommended dose and administration of golimumab for the treatment of patients with moderately-to-severely active RA, active PsA, and active AS, is 50 mg self-administered by subcutaneous injection once a month. Patients treated with golimumab may receive vaccinations, except for live vaccines. No data are available on the response to live vaccination or the risk of infection, or transmission of infection after the administration of live vaccines to patients receiving golimumab. The most common adverse reactions to golimumab include upper respiratory tract infection, sore throat and nasal congestion.

A black box warning is included in the golimumab label. The warning states that patients treated with golimumab are at increased risk for serious infections. Tuberculosis (frequently disseminated or extrapulmonary at clinical presentation), invasive fungal infections, and other opportunistic infections, have been observed in patients receiving golimumab. Some of these infections have been fatal. Most patients who developed these infections were taking concomitant immunosuppressants (e.g., MTX or corticosteroids). Patients should be tested for latent tuberculosis before golimumab use and during therapy. Treatment for latent infection should be initiated prior to golimumab use. In addition, patients should be monitored for signs and symptoms of infection during and after treatment with golimumab, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.

Golimumab should not be used with abatacept or anakinra. In controlled trials, the concurrent administration of another TNF-blocker, including golimumab, and abatacept was associated with a higher proportion of serious infections without additional clinical benefit. The concurrent administration of anakinra and another TNF-blocker, including golimumab, was associated with a higher rate of serious infection and neutropenia with no additional clinical benefits compared with the TNF-blocker alone.

The U.S. Food and Drug Administration (FDA) has approved an intravenous formulation of golimumab, Simponi Aria, for the treatment of adults with moderately to severely active rheumatoid arthritis (RA) in combination with methotrexate. The Simponi Aria dose regimen is 2 mg/kg given as an intravenous infusion at weeks 0 and 4, then every 8 weeks thereafter. The infusion is given over a 30-minute period, providing a short infusion time for patients.

The approval is supported by findings from the Phase 3 Trial of Golimumab, an Anti-TNF-alpha Monoclonal Antibody, Administered Intravenously, in Subjects with Active Rheumatoid Arthritis Despite Methotrexate Therapy (GO-FURTHER) trial, a Phase 3, international multicenter, double-blind, placebo-controlled study including 592 adults with RA designed to compare ACR 20 response at week 14 in patients receiving an I.V. golimumab infusion plus methotrexate compared with patients receiving placebo infusions plus methotrexate. The trial included patients diagnosed with moderately to severely active RA who had at least six tender and six swollen joints at screening and baseline, had elevated CRP levels at screening and who had been receiving background methotrexate for at least 3 months. Patients were randomized 2:1 to receive a 30 (+/- 10) minute I.V. infusion of golimumab 2 mg/kg or placebo at weeks 0, 4, and then every 8 weeks; in both treatment arms, methotrexate was taken. The primary endpoint of the study was the proportion of subjects who had at least 20 percent improvement in American College of Rheumatology criteria (ACR 20) at week 14. At week 16, patients receiving placebo with less than 10 percent improvement in combined swollen and tender joint counts from baseline qualified for early escape and received I.V. golimumab 2 mg/kg infusions at week 16 and week 20 and every 8 weeks subsequent; patients receiving golimumab who qualified for early escape remained on their golimumab therapy. All patients receiving placebo crossed over to I.V. golimumab at week 24. Radiographs of the hands and feet were taken at baseline, week 24 (week 16 for early escape participants regardless of whether they had been randomized to placebo or golimumab) and week 52, and were scored using the van der Heijde-Sharp (vH-S) score, an X-ray measure of joint destruction, including joint erosion and joint space narrowing in which higher scores indicate greater structural damage.
Results from the trial revealed 59 percent (n = 231/395) of patients receiving treatment with I.V. golimumab plus methotrexate versus 25 percent of patients receiving placebo plus methotrexate (n = 49/197) (a difference with 95 percent CI 25.9, 41.4) experienced significant improvements in signs and symptoms at week 14, as demonstrated by at least 20 percent improvement in American College of Rheumatology criteria (ACR 20). A higher proportion of patients receiving I.V. golimumab plus methotrexate achieved at least a 50 percent improvement in ACR criteria (ACR 50) compared with patients receiving placebo plus methotrexate at week 14 (30 percent versus 9 percent, respectively, a difference with 95 percent CI 15.3, 27.2). Significant improvements in ACR 20 were observed as early as week 2, after a single I.V. golimumab infusion, as 33 percent of patients achieved an ACR 20 response versus 12 percent 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. At week 24, patients receiving I.V. golimumab 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 I.V. golimumab treated patients versus 1.20 in placebo patients who crossed over to I.V. golimumab at either week 16 or 24.

Through week 24, adverse events (AEs) occurred in 53 percent of patients receiving I.V. golimumab and 49 percent of patients receiving placebo, and serious AEs were reported in more I.V. golimumab-treated patients (4 percent) than placebo-treated patients (2 percent). In the controlled phase of the trial through Week 24, infections were observed in 27 percent of I.V. golimumab-treated patients compared with 24 percent of placebo-treated patients, and serious infections were observed in 0.9 percent of I.V. golimumab-treated patients and 0.0 percent of placebo-treated patients. One case of tuberculosis and one death, a myocardial infarction secondary to community-acquired pneumonia, were reported in the I.V. golimumab group. In addition, one death was reported among placebo-treated patients through week 24. Through week 24, the proportions of infusions with infusion reactions were 1.1 percent and 0.2 percent, respectively.

Sandborn et al (2014) performed a phase 3, double-blind trial of patients who completed golimumab induction trials (PURSUIT). Patients who responded to induction therapy with golimumab (n = 464) were randomly assigned to groups given placebo or injections of 50 or 100 mg golimumab every 4 weeks through week 52. Patients who responded to placebo in the induction study continued to receive placebo. Non-responders in the induction study received 100 mg golimumab. The primary endpoint was clinical response maintained through week 54; secondary endpoints included clinical remission and mucosal healing at both weeks 30 and 54. Clinical response was maintained through week 54 in 47.1 % of patients receiving 50 mg golimumab, 50.6 % receiving 100 mg golimumab, and 31.4 % receiving placebo (p = 0.010 and p < 0.001, respectively). At weeks 30 and 54, a higher percentage of patients who received 100 mg golimumab were in clinical remission and had mucosal healing (28.6 % and 43.5 %) than patients given placebo (15.4 % and 26.9 %; p = 0.003 and p = 0.001, respectively) or 50 mg golimumab (23.5 % and 41.8 %, respectively). Percentages of serious adverse events were 7.7 %, 8.4 %, and 14.3 % among patients given placebo, 50 mg, or 100 mg golimumab, respectively; percentages of serious infections were 1.9 %, 3.2 %, and 3.2 %, respectively. Among all patients given golimumab in the study, 3 died (from sepsis, tuberculosis, and cardiac failure, all in patients who received 100 mg golimumab) and 4 developed active tuberculosis. The authors concluded that golimumab (50 mg or 100 mg) maintained clinical response through week 54 in patients who responded to induction therapy with golimumab and had moderately-to-severely active UC; patients who received 100 mg golimumab had clinical remission and mucosal healing at weeks 30 and 54. Safety was consistent with that reported for other TNFα-antagonists and golimumab in other approved indications.

Sanchez-Cano et al (2013) noted 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, spondyloarthritis, 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) Behçet's disease, (ii) sarcoidosis, and (iii) non-infectious uveitis. 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.

Judson et al (2014) noted that sarcoidosis is characterized by non-caseating granulomas that secrete pro-inflammatory cytokines, including interleukin (IL)-12, IL-23, and TNF-alpha. Ustekinumab and golimumab are monoclonal antibodies that specifically inhibit IL-12/IL-23 and TNF-α, respectively. These researchers examined the safety and effectiveness of ustekinumab or golimumab in patients with chronic sarcoidosis. Patients with chronic pulmonary sarcoidosis (lung group) and/or skin sarcoidosis (skin group) received either 180 mg ustekinumab at week 0 followed by 90 mg every 8 weeks, 200 mg golimumab at week 0 followed by 100 mg every 4 weeks, or placebo. Patients underwent corticosteroid tapering between weeks 16 and 28. The primary endpoint was week 16 change in percentage predicted forced vital capacity (ΔFVC % pred) in the lung group. Major secondary endpoints were: week 28 for ΔFVC % pred, 6-min walking distance, St George’s Respiratory Questionnaire (lung group), and Skin Physician Global Assessment response (skin group). At week 16, no significant differences were observed in ΔFVC % pred with ustekinumab (-0.15, p = 0.13) or golimumab (1.15, p = 0.54) compared with placebo (2.02). At week 28, there were no significant improvements in the major secondary endpoints, although a non-significant numerically greater Skin Physician Global Assessment response was observed following golimumab treatment (53 %) when compared with the placebo (30 %). Serious adverse events were similar in all treatment groups. The authors concluded that although treatment was well-tolerated, neither ustekinumab nor golimumab demonstrated effectiveness in pulmonary sarcoidosis. However, trends towards improvement were observed with golimumab in some dermatological end-points.

In a non-randomized, retrospective, multi-centered, interventional case-series study, Cordero-Coma et al (2014) evaluated the short-term safety and effectiveness of GLM for treatment of immune-mediated uveitis resistant to previous immunosuppressive therapy. A total of 13 patients with different types of uveitis that were resistant to treatment with at least 2 previous immunosuppressants were included in this study. All included patients were treated with GLM (50 mg every 4 weeks) during at least 6 months. Clinical evaluation and treatment-related side effects were assessed at least 4 times in all included patients. Eight men and 5 women (22 affected eyes) with a median age of 30 years (range of 20 to 38) and active immune-mediated uveitides were studied. Golimumab was used in combination with conventional immunosuppressants in 7 patients (53.8 %). Golimumab therapy achieved complete control of inflammation in 12/13 patients (92.3 %) after 6 months of treatment. There was a statistically significant improvement in mean best corrected visual acuity (BCVA) (0.60 versus 0.68, p = 0.009) and mean 1 mm central retinal thickness (317 versus 261.2 μ, p = 0.05) at the 6-month endpoint when compared to basal values. No major systemic adverse effects associated with GLM therapy were observed. The authors concluded that GLM is a new and promising therapeutic option for patients with severe and refractory uveitis.

In a retrospective study, Miserocchi et al (2014) evaluated the long-term effectiveness of GLM in patients with severe recalcitrant uveitis who had inadequate response to previous biologics. A total of 13 patients with juvenile idiopathic arthritis, 4 with HLA-B27-associated uveitis were included in this study. Indication for treatment was active uveitis despite biologics; GLM dosing was 50 mg monthly/subcutaneously. Main outcome measures included uveitis activity, visual acuity improvement, decrease in systemic therapy (corticosteroids/immunosuppressants), and adverse events. Of 17 patients (34 affected eyes), response to GLM was seen in 14 patients; at last visit uveitis was inactive in
12 patients. Three patients were non-responders. Mean follow-up time on GLM was 21.9 months. Visual acuity remained stable in 26 eyes, improved in 7, and worsened in 1. Mean systemic prednisolone dose before and after GLM was 12.5 to 3.5 mg/day. One patient developed pulmonary infection. The authors concluded that GLM may be a promising new therapeutic option for severe uveitis patients who have not responded to other biologics.

Furthermore, an expert panel's recommendations for the use of anti-TNF biologic agents in patients with ocular inflammatory disorders including Behcet's disease, panuveitis, posterior uveitis, and scleritis (Levy-Clarke et al, 2014) does not mention golimumab as a therapeutic option.

Appendix

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic Name</th>
<th>FDA Labeled Indications</th>
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<td>Actemra</td>
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CPT Codes / HCPCS Codes / ICD-9 Codes

Other CPT codes related to the CPB:

96365 - 96368  Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug)
96369 - 96371  Subcutaneous infusion for therapy or prophylaxis (specify substance or drug)
96372  Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular
96374  Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); intravenous push, single or initial substance/drug
96379  Unlisted therapeutic, prophylactic, or diagnostic intravenous or intra-arterial injection or infusion

HCPCS codes covered if selection criteria are met:

There is no specific code for subcutaneously administered golimumab (Simponi):

J1602  Injection, golimumab, 1 mg, for intravenous use [Simponi Aria only]

Other HCPCS codes related to the CPB:

J1020  Injection, methylprednisolone acetate, 20 mg
J1030  Injection, methylprednisolone acetate, 40 mg
J1040  Injection, methylprednisolone acetate, 80 mg
J1094  Injection, dexamethasone acetate, 1 mg
J1600  Injection, gold sodium thiomalate, up to 50 mg
J2920  Injection, methylprednisolone sodium succinate, up to 40 mg [Solu-Medrol]
J2930  Injection, methylprednisolone sodium succinate, up to 125 mg [Solu-Medrol]
J7500  Azathioprine, oral, 50 mg
J7501  Azathioprine, parenteral, 100 mg
J7502  Cyclosporine, oral, 100 mg
J7506  Prednisone, oral, per 5 mg
J7509  Methylprednisolone, oral, per 4 mg
J7510  Prednisolone, oral, per 5 mg
J7515  Cyclosporine, oral, 25 mg
J7516  Cyclosporine, parenteral, 250 mg
J8530  Cyclophosphamide, oral, 25 mg
J8540  Dexamethasone, oral, 0.25 mg
J8610  Methotrexate, oral, 2.5 mg
J9070  Cyclophosphamide, 100 mg
J9250  Methotrexate sodium, 5 mg
J9260  Methotrexate sodium, 50 mg
S0108  Mercaptopurine, oral, 50 mg

ICD-9 codes covered if selection criteria are met for I.V. golimumab (Simponi Aria):
714.0 - 714.33  Rheumatoid arthritis

ICD-9 codes not covered for indications listed in the CPB (not all inclusive):
364.00 - 364.9  Disorders of iris and ciliary body [ocular inflammatory disorders]

ICD-9 codes covered if selection criteria are met for subcutaneously administered golimumab (Simponi):
556.0 - 556.9  Ulcerative colitis
696.0 - 696.1  Psoriatic arthropathy and other psoriasis [see CPB 658 Psoriasis: Biological Therapies]
714.0 - 714.33  Rheumatoid arthritis
720.0  Ankylosing spondylitis

ICD-9 codes not covered for indications listed in the CPB (not all inclusive):
135  Sarcoidosis
364.00 - 364.9  Disorders of iris and ciliary body [ocular inflammatory disorders]
493.00 - 493.92  Asthma

The above policy is based on the following references:


