



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans administered by Great-West Healthcare, which is now a part of CIGNA.

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Subject **Adalimumab (Humira®)**

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Hyperlink to Related Coverage Policies

Enbrel®
Kineret®
Orencia®
Remicade®
Rituxan®

INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans as well as benefit plans formerly administered by Great-West Healthcare. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2009 CIGNA

Coverage Policy

CIGNA covers adalimumab (Humira®) as medically necessary for treatment of ANY of the conditions listed when the associated criteria are met:

- active rheumatoid arthritis (RA) in adults (≥18 years of age) **OR** polyarticular juvenile idiopathic arthritis (JIA) in individuals 4–17 years of age for **EITHER** of the following indications:
 - history of a beneficial clinical response to adalimumab therapy for RA/JIA condition
 - inadequate response, intolerance, or contraindication to at least one disease-modifying anti-rheumatic drugs (DMARDs) (i.e., Methotrexate (MTX) Azathioprine, gold, Hydroxychloroquine, Penicillamine, Sulfasalazine) as evidenced by documented disease progression based on the assessment of disease activity using **ANY** of the following:
 - progression of radiographic damage of involved joints
 - Health Assessment Questionnaire Disease Index (HAQ-DI)
 - Visual Analogue scale (VAS)
 - Likert scales of global response to pain by the individual/doctor
 - Global Arthritis Score (GAS)
 - Clinical Disease Activity Index (CDAI)
 - Simplified Disease Activity Index (SDAI)
 - Disease Activity Scale (DAS) score
 - Disease Activity Score based on 28-joint evaluation (DAS28) score

Initial authorization: 16 weeks when criteria are met. Subsequent requests: After 16 weeks, approval of continuation of therapy for ONE YEAR when there is a beneficial clinical response to treatment and documented improvement indicated by ANY of the following:

- 20% improvement according to ACR response criteria
 - HAQ-DI
 - VAS
 - Likert scales of global response to pain by the individual/doctor
 - GAS
 - CDAI
 - SDAI
 - DAS score
 - DAS28 score
-
- psoriatic arthritis **AND EITHER** of the following:
 - history of beneficial clinical response to adalimumab therapy
 - failure, contraindication, or intolerance to methotrexate therapy

 - ankylosing spondylitis **AND EITHER** of the following:
 - history of beneficial clinical response to adalimumab therapy
 - failure, contraindication, or intolerance to nonsteroidal anti-inflammatory drugs (NSAIDs)

 - active Crohn's disease **AND ANY** of the following:
 - history of beneficial clinical response to adalimumab therapy
 - failure, inadequate response, contraindication or intolerance to conventional therapies (aminosalicylate, corticosteroids, or immunomodulators)
 - failure, contraindication, or intolerance to infliximab (Remicade®)

 - chronic plaque psoriasis in adults (≥18 years of age) **AND EITHER** of the following:
 - history of beneficial clinical response to adalimumab therapy
 - individual is a candidate for, or has previously received ONE of the following:
 - Systemic therapy (e.g., methotrexate, cyclosporin, soriatane)
 - Phototherapy [narrow or broad band ultraviolet B (UVB), or psoralen plus ultraviolet A (PUVA)]

Note: For chronic plaque psoriasis in individuals with no history of beneficial clinical response, the initial approval limits will be three months with the ability to increase to twelve-month intervals, providing therapeutic response was achieved. No limited authorization for individuals who are diagnosed with rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), psoriatic arthritis, ankylosing spondylitis, or Crohn's disease and have a history of beneficial clinical response.

General Background

U.S. Food and Drug Administration (FDA) Approved Indication

Adalimumab is a tumor necrosis factor (TNF) blocker indicated for the treatment of following:

- **Rheumatoid Arthritis (RA)** - used alone or in combination with methotrexate or other disease-modifying anti-rheumatic drugs (DMARDs), to reduce signs and symptoms, including major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active disease

- **Juvenile Idiopathic Arthritis (JIA)** - reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients ages 4 years of age and older. Adalimumab can be used alone or in combination with methotrexate.
- **Psoriatic Arthritis** - reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function
- **Ankylosing Spondylitis** - reducing signs and symptoms in patients with active disease
- **Crohn's Disease** - reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. Reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.
- **Plaque Psoriasis** - treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate.

FDA Recommended Dosing

Adult patients with rheumatoid arthritis (RA), psoriatic arthritis, or ankylosing spondylitis: 40 mg administered every other week as a subcutaneous injection.

JIA in patients 4 to 17 years of age is based on weight as follows: pediatric patients (4 to 17 years) dose 15 kg (33 lbs) to <30 kg (66 lbs) - 20 mg every other week (20 mg prefilled syringe); ≥30 kg (66 lbs) - 40 mg every other week (HUMIRA Pen or 40 mg prefilled syringe). Limited data are available for adalimumab treatment in pediatric patients with a weight below 15 kg (33 lbs).

Crohn's disease: 160 mg at week 0 initial dosing, and then 80 mg dose at week two, followed by maintenance dose of 40 mg every other week beginning at week four. The initial dose may be given as four injections on one day, or divided over two days.

Chronic plaque psoriasis: 80 mg initial dose at week 0 followed by 40 mg every other week starting one week after initial dose. The use of adalimumab in moderate to severe chronic plaque psoriasis beyond one year has not been evaluated in controlled clinical studies.

Adalimumab binds specifically to TNF-alpha and blocks its interaction with the cell surface TNF receptors. Adalimumab also lyses surface TNF expressing cells in vitro in the presence of complement. TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Methotrexate, glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, or other disease-modifying antirheumatic drugs (DMARDs) may be continued during treatment with adalimumab. In RA, some patients not taking concomitant methotrexate may derive additional benefit from increasing the dosing frequency of adalimumab to 40 mg every week.

Guidelines

The American College of Rheumatology (ACR) 2008 recommendations published in June 15, 2008 issue of Arthritis Care & Research include the use of nonbiologic and biologic therapies in patients with RA when starting or resuming these therapies. The 2008 ACR recommendations address five key areas including: the indications for use, monitoring for side-effects, assessing the clinical response, screening for tuberculosis which is a risk factor associated with biologic DMARDs, and the roles of cost and patient preference in choosing biologic agents under certain circumstances (i.e. high disease activity). The duration of RA disease duration, disease severity, and prognostic features were also considered when developing these recommendations. According to ACR guideline, it is important that RA patients be seen regularly to assess disease activity, evaluate disease severity, and determine whether alternative therapies are warranted. Because there was no evidence to support a specific recommendation on the frequency of provider visits, a specific and potentially arbitrary time frame is not recommended at this point. However, based on these recommendations, commonly used but not exclusive tools to assess the RA disease activity include: Disease Activity Score (DAS) in 28 joints, Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), Rheumatoid Arthritis Disease Activity Index, Patient Activity Scale (PAS), and Routine Assessment Patient Index Data. In addition it is recommended to use the combinations of commonly used but not exclusive prognostic factors to evaluate the patients with RA, including: Health Assessment Questionnaire (HAQ) score, Evidence of radiographic erosions, Elevated

erythrocyte sedimentation rate, Elevated C-reactive protein level, and elevated levels of rheumatoid factor (RF) and/or anti-cyclic citrullinated peptide (anti-CCP) antibodies. Due to the absence of a single “gold standard” measure, multiple measures or pooled indices are used to determine a diagnosis, estimate prognosis, and to assess and monitor disease activity and response to treatment. Other commonly used measures in the clinical settings include: Visual Analogue scale (VAS), Likert scales of global response to pain by the patient/doctor, and Global Arthritis Score (GAS).

Although there are other nonbiologic and biologic DMARDs that are either approved by the FDA or occasionally used for treating RA, only the nonbiologic agents hydroxychloroquine, leflunomide, methotrexate, minocycline, and sulfasalazine, and the biologics abatacept, adalimumab, etanercept, infliximab, and rituximab are included in the 2008 ACR recommendations. Following are the 2008 ACR recommendations for nonbiologic and biologic DMARD use in RA:

- Initiating methotrexate or leflunomide therapy is recommended for most RA patients.
- Methotrexate plus hydroxychloroquine is endorsed for patients with moderate to high disease activity.
- The triple DMARD combination of methotrexate plus hydroxychloroquine plus sulfasalazine for patients with poor prognostic features and moderate to high levels of disease activity.
- Prescribing anti-TNF α agents including etanercept, infliximab, or adalimumab, along with methotrexate in early RA (less than 3 months) only for patients with high disease activity who had never received DMARDs. In intermediate- and longer-duration RA, anti-TNF α agents were recommended for patients who had failed to respond adequately to methotrexate therapy.
- Reserving abatacept and rituximab for patients with at least moderate disease activity and poor disease prognosis for whom methotrexate in combination with or sequential administration of other nonbiologic DMARDs led to an inadequate response.
- Avoiding the initiation or resumption of treatment with methotrexate, leflunomide, or biologic agents for patients with active bacterial infection, active herpes-zoster viral infection, active or latent tuberculosis, or acute or chronic hepatitis B or C.
- Not prescribing anti-TNF α agents to patients with a history of heart failure, with a history of lymphoma, or with multiple sclerosis or demyelinating disorders.
- Avoiding the initiation or resumption of methotrexate, leflunomide, or minocycline for RA patients planning for pregnancy and throughout the duration of pregnancy and breastfeeding.

According to 2008 ACR, these recommendations are not meant to take the place of personalized patient care and are intended to provide guidance based on clinical evidence rather than prohibit appropriate therapies or limit a physician's clinical judgment. Additionally, these recommendations are extensive but not comprehensive.

In clinical practice, the severity of a patient's psoriasis is evaluated by combining the objective assessment (e.g. body surface area (BSA) of involvement, disease location, thickness) and subjective assessment of the physical, financial, and emotional impact of the disease on the patient's life. This subjective assessment is combined with the physician's global assessment of psoriasis to determine psoriasis severity and appropriate therapy. The National Psoriasis Foundation Medical Board (Pariser, et al., 2007) recommends two-tiered system that categorizes patients based on treatment plans as candidates for localized therapy or for systemic therapy and/or phototherapy. Localized therapy, which includes topical treatments and excimer laser treatments, is recommended for patients with psoriasis that affects less than 5% BSA. Appropriate therapies include, but are not restricted to, topical corticosteroids, topical cholecalciferol analogs, combinations of these 2, topical retinoids, tar preparations, anthralin, keratolytics, and excimer (UV-B) laser treatments. In general, the effects of topical therapy should become evident within the first two to three weeks of use. Clearing of scale is usually observed first, followed by flattening of the treated plaques. Resolution of erythema may take six to eight weeks. Systemic therapy and/or phototherapy, which includes broad and narrowband phototherapy, photochemotherapy (PUVA), systemic agents, and biologics, is recommended for patients with psoriasis affecting greater than 5% BSA, for those with less than 5% BSA affected in vulnerable areas, such as the face, genitals, hands or feet, and for other forms of psoriasis, including but not limited to erythrodermic, pustular, and guttate. In addition, patients with limited affected areas and inadequate response to localized therapy or impairment in physical or mental functioning should also be considered candidates for systemic and/or phototherapy treatment.

The American Academy of Dermatology (AAD) published a consensus statement (Callen, et al., 2003) on psoriasis therapies. The document is intended to be used as a guide to the evaluation and treatments of

psoriasis until evidence based guidelines are developed. Within this document, the authors state that BSA should not generally be used to determine which therapy to select; moderate and severe disease overlap and individuals with limited disease can be considered moderate for the purposes of selecting a therapy. Topical therapies are recommended for limited plaque disease. For moderate to severe disease, the AAD recommends phototherapy, targeted phototherapy, narrowband UVB, photochemotherapy with psoralen and UVA light (PUVA), topicals and systemic treatments.

Clinical Efficacy

- **Rheumatoid Arthritis (RA)**

Adalimumab has been evaluated for the management of rheumatoid arthritis (RA) in randomized, double-blind clinical trials in adults with active disease as defined by the American College of Rheumatology (ACR). Adalimumab was administered in combination with methotrexate (MTX), in combination with a disease-modifying antirheumatic drug (DMARD) therapy and/or other antirheumatic agents, or as monotherapy in these trials.

In a randomized, placebo-controlled trial in adults with active RA receiving antirheumatic therapy (e.g., a DMARD, nonsteroidal anti-inflammatory agents [NSAIDs], corticosteroid) at study entry and during the study, adalimumab, given at a dosage of 40 mg once every other week for 24 weeks, was associated with an ACR 20 in 53% of patients; an ACR 20 was reported in 35% of placebo-treated patients. In another randomized, placebo-controlled trial in adults with active RA who had not responded adequately to one or more DMARDs, therapy with adalimumab 40 mg once every other week (as monotherapy) for 26 weeks was associated with an ACR 20, 50, or 70 in 46, 22, or 12% of patients, respectively, and therapy with adalimumab 40 mg every week for 26 weeks was associated with an ACR 20, 50, or 70 in 53%, 35%, or 18% of patients, respectively. In this trial, an ACR 20, 50, or 70 was reported in 19%, 8%, or 2% of patients receiving placebo, respectively.

Data from the Anti-TNF Research Study Program of the Monoclonal Antibody D2E7 in Rheumatoid Arthritis (ARMADA) trial show the addition of adalimumab to MTX in patients with active RA despite MTX therapy provided significant, rapid, and sustained improvement in disease activity over 24 weeks compared to MTX plus placebo. The ARMADA trial was a pivotal trial included in the regulatory application for adalimumab. It was designed as a 24-week, randomized, double-blind study of 271 patients with active RA despite current treatment with MTX. Patients were randomly assigned to receive subcutaneous injections of HUMIRA (20 mg, 40 mg, or 80 mg doses) or placebo every other week while continuing to take MTX. The efficacy of adalimumab was assessed using the American College of Rheumatology ACR 20 response, which represents a 20% improvement in clinical measures such as the number of tender and swollen joints. ACR 50 and ACR 70 response rates were also measured. At 24 weeks, more than half of the patients receiving adalimumab 40 mg every other week achieved an ACR 20 and ACR 50 response (67.2% and 55.2%), which was significantly greater than the response seen in patients receiving placebo (14.5% and 8.1%). Additionally, more than one in four patients achieved the ACR 70 response (26.9% vs. 4.8% for placebo), which is the closest clinical measure to remission of RA signs and symptoms. Responses were rapid, with some patients reaching an ACR 20 response after one week of treatment (25.4% of patients receiving adalimumab 40 mg every other week vs. 6.5% with placebo). Patients receiving adalimumab plus MTX showed a statistically significant improvement at 24 weeks over baseline in each of the seven ACR core components, including tender joint count, swollen joint count, patient pain assessment, and patient global assessment of disease compared to patients receiving MTX plus placebo.

- **Polyarticular Juvenile Idiopathic Arthritis (JIA)**

The safety and efficacy of adalimumab were assessed in a multicenter, randomized, withdrawal, double-blind, parallel-group study in 171 children (4 to 17 years of age) with JIA. In the study, the patients were stratified into two groups: MTX-treated or non-MTX-treated. All subjects had to show signs of active moderate or severe disease despite previous treatment with NSAIDs, analgesics, corticosteroids, or DMARDs. Subjects who received prior treatment with any biologic DMARDs were excluded from the study. The study included four phases: an open-label lead in phase (OL-LI; 16 weeks), a double-blind randomized withdrawal phase (DB; 32 weeks), an open-label extension phase (OLE-BSA; up to 136 weeks), and an open-label fixed dose phase (OLE-FD; 16 weeks). In the first three phases of the study, adalimumab was administered based on body surface area at a dose of 24 mg/m² up to a maximum total body dose of 40 mg subcutaneously (SC) every other week. In the OLE-FD phase, the patients

were treated with 20 mg of adalimumab every other week if their weight was less than 30 kg and with 40 mg of adalimumab every other week if their weight was 30 kg or greater. Patients remained on stable doses of NSAIDs and/or prednisone (≤ 0.2 mg/kg/day or 10 mg/day maximum). Patients demonstrating a Pediatric ACR 30 response at the end of OL-LI phase were randomized into the double blind (DB) phase of the study and received either adalimumab or placebo every other week for 32 weeks or until disease flare. Disease flare was defined as a worsening of $\geq 30\%$ from baseline in ≥ 3 of 6 Pediatric ACR core criteria, ≥ 2 active joints, and improvement of $>30\%$ in no more than 1 of the 6 criteria. After 32 weeks or at the time of disease flare during the DB phase, patients were treated in the open-label extension phase based on the BSA regimen (OLE-BSA), before converting to a fixed dose regimen based on body weight (OLE-FD phase). At the end of the 16-week OL-LI phase, 94% of the patients in the MTX stratum and 74% of the patients in the non-MTX stratum were Pediatric ACR 30 responders. In the DB phase significantly fewer patients who received adalimumab experienced disease flare compared to placebo, both without MTX (43% vs. 71%) and with MTX (37% vs. 65%). More patients treated with adalimumab continued to show pediatric ACR 30/50/70 responses at week 48 compared to patients treated with placebo. Pediatric ACR responses were maintained for up to two years in the OLE phase in patients who received adalimumab throughout the study.

- **Psoriatic Arthritis**

A placebo-controlled, double-blind study assessed the efficacy and tolerability of adalimumab in 313 adults with active psoriatic arthritis (defined as three or more swollen joints and three or more tender joints) who had failed therapy with NSAIDs. Patients received 40 mg of adalimumab or placebo administered subcutaneously every other week. Efficacy was assessed using ACR 20 response (20% improvement in tender and swollen joint count and other clinical measures), one of the primary study endpoints. Secondary endpoints included ACR 50/70, Psoriasis Area and Severity Index (PASI) measurement, which measures the extent and severity of psoriasis in patients with more than 3% body surface area involvement and other clinical assessments. In the adalimumab treatment group, improvement in arthritis signs and symptoms was rapid, with 27% of patients achieving an ACR 20 response after two weeks and 52% of patients achieving an ACR 20 response after just four weeks, compared to 6% and 9%, respectively, for patients taking placebo. At 24 weeks, 39% of patients treated with adalimumab achieved an ACR 50 response and 23% achieved ACR 70, compared to 6% and 1%, respectively, in the placebo group. In patients with more than 3% body surface area involvement, 42% of patients taking adalimumab achieved a PASI 90 response at 24 weeks, which reflects at least 90% improvement in psoriasis symptoms assessed by the PASI. Nearly one-third of the patients achieved 90% improvement at the week 12 visit. At 24 weeks, 59% of patients in the adalimumab arm achieved a PASI 75 response (75% improvement), compared with 1% of patients taking placebo.

- **Ankylosing Spondylitis**

A randomized, placebo-controlled, double-blind Phase III study conducted in Europe and the United States evaluated the safety and efficacy of adalimumab in patients with active ankylosing spondylitis (AS). The primary efficacy endpoint was the percentage of patients with a 20% response according to the ASAssessment in Ankylosing Spondylitis International Working Group criteria for improvement (ASAS20) at week 12. Results showed that Humira was successful in reducing pain and inflammation in patients with AS after 12 weeks of treatment, with 58.2% of adalimumab-treated patients who achieved an ASAS20 response, compared with 20.6% of placebo-treated patients ($p < 0.001$). Other findings demonstrated significant improvement in measures of disease activity for many patients treated with Humira that were first observed at week two and maintained through 24 weeks. Adalimumab significantly improved virtually all measures of disease activity, including patients' and physicians' global assessments of disease activity, total and nocturnal back pain and inflammation. Adalimumab-treated patients (22.1%) achieved partial remission more than placebo-treated patients (5.6%) ($p < 0.001$). More adverse events were reported with adalimumab-treated patients (75%) than placebo-treated patients (59.8%) ($p < 0.05$), but there was no statistically significant difference in the incidence of infections.

- **Crohn's Disease**

A four-week, randomized, double-blind, placebo-controlled, multicenter trial [CLASSIC (Clinical Assessment of Adalimumab Safety and efficacy Studied as an Induction therapy in Crohn's)] evaluated the efficacy and tolerability of adalimumab to induce remission in 299 patients with active Crohn's disease. In this study, patients with moderately to severely active Crohn's disease (Crohn's disease activity index [CDAI] score ≥ 220) were randomized to treatment with placebo, or to one of three

loading-dose strategies with adalimumab. The three adalimumab dosing regimens were as follows: (1) 40-mg loading dose with 20-mg dose at week two (target dose 20 mg every other week with serum concentration > 2 mcg/mL, anticipated to be an ineffective dose); (2) 80-mg loading dose with 40-mg dose at week two (target dose 40 mg every other week with serum concentration 4–8 mcg/mL, anticipated to be an effective dose); and (3) 160-mg loading dose with 80-mg dose at week two (target dose 40 mg weekly with serum concentration >10 mcg/mL, anticipated to be a maximally effective dose). The primary study endpoint was induction of clinical remission (CDAI score < 150). The rates of remission at week four in the adalimumab 40 mg/20 mg, 80 mg/40 mg, and 160/80 mg groups were 18% (p=0.36), 24% (p=0.06), and 36% (p=0.001); remission was 12% in the placebo group. A pharmacokinetic substudy from CLASSIC 1 demonstrated that the week four adalimumab concentrations were 2.79 mcg/mL in the 40 mg/20 mg group, 5.65 mcg/mL in the 80 mg/40 mg group, and 12.61 mcg/mL in the 160 mg/80 mg group, indicating that the target serum concentrations were achieved.

Two hundred seventy-six of the 299 patients who participated in CLASSIC I enrolled in CLASSIC II. In CLASSIC II, all patients received adalimumab 40 mg at week 0 (week 4 of Classic I) and week two. Fifty-five patients who were in remission (CDAI < 150) at both week 0 and week 4 were re-randomized to receive adalimumab 40 mg every other week, adalimumab 40 mg weekly, or placebo for up to one year. The results from this 55-patient controlled trial are not yet available. The remaining 220 patients not in remission at week 0 and/or week 4 in CLASSIC II received additional open-label adalimumab 40 mg every other week. Dose escalation to 40 mg weekly was allowed for flare or nonresponse. The results of open-label adalimumab therapy through week 24 in these 220 patients who initially failed to achieve remission during CLASSIC I, and/or during the first four weeks of open-label therapy with adalimumab during CLASSIC II, were also reported during the Digestive Disease Week (DDW) meeting. During CLASSIC II, the rates of clinical response (reduction from baseline CDAI of ≥ 70) and remission (CDAI < 150) at week 24 in patients who initially failed to achieve remission were 33% and 78%, respectively. Overall, 71% of patients treated in the open-label portion of the study continued on therapy at week 24. Of these patients, two-thirds continued on adalimumab 40 mg every other week, and one-third had dose escalation to 40 mg weekly. Associated adverse events were mild to moderate in severity. The most common were exacerbations of Crohn's disease and infections.

The CHARM trial (Crohn's trial of the fully Human antibody Adalimumab for Remission Maintenance), a double-blind, placebo-controlled 56-week trial, evaluated the efficacy and safety of adalimumab taken weekly and every other week, versus placebo, in maintaining clinical remission (CDAI<150) at week 26 and week 56 in patients with moderate to severely active CD (CDAI 220–450) who responded to open-label induction therapy. Co-primary endpoints in CHARM were clinical remission rates at week 26 and week 56. The data show significantly higher remission rates (CDAI<150) at weeks 26 and 56 versus placebo, among patients with a decrease in CDAI greater than or equal to 70 points at week four. A total of 854 patients enrolled in this study were treated with a loading-dose regimen of adalimumab 80 mg at week 0 and 40 mg at week 2. Four hundred ninety-nine patients (58%) who responded at week 4 (defined as a decrease in the CDAI score ≥ 70 points) were randomized to treatment through week 56 with adalimumab 40 mg every other week, adalimumab 40 mg weekly, or placebo. The rates of clinical remission among responders at week 26 were 40% (p<0.001) for adalimumab 40 mg every other week, and 47% (p<0.001) for adalimumab 40 mg weekly, and 17% for placebo group. The rates of clinical remission among responders at week 56 were 12%, 36% (p<0.001), and 41% (p<0.001) for placebo, adalimumab 40 mg every other week, and adalimumab 40 mg weekly, respectively. Additional results from CHARM on the efficacy of adalimumab in the long-term maintenance of remission in patients with Crohn's disease without corticosteroid use showed that maintenance adalimumab therapy allowed significant percentages of patients to maintain steroid-free remission (off steroid therapy ≥ 90 days) at week 26 (placebo (3%), adalimumab 40 mg every other week (19%), and adalimumab 40 mg weekly (15%) [p<0.05]), and at week 56 (6% on placebo, 29% of patients receiving adalimumab 40 mg every other week, and 20% receiving adalimumab 40 mg weekly [p \leq 0.05]).

- **Chronic Plaque Psoriasis**

The safety and efficacy of adalimumab were assessed in randomized, double-blind, placebo-controlled studies in 1696 adult patients with moderate to severe chronic plaque psoriasis who were candidates for systemic therapy or phototherapy. Study Ps-I evaluated 1212 patients with chronic plaque psoriasis with

≥10% body surface area (BSA) involvement, Physician's Global Assessment (PGA) of at least moderate disease severity, and Psoriasis Area and Severity Index (PASI) ≥12 within three treatment periods. In period A, patients received placebo or HUMIRA at an initial dose of 80 mg at Week 0 followed by a dose of 40 mg every other week starting at Week 1. After 16 weeks of therapy, patients who achieved at least a PASI 75 response at Week 16, defined as a PASI score improvement of at least 75% relative to baseline, entered period B and received open-label 40 mg HUMIRA every other week. After 17 weeks of open label therapy, patients who maintained at least a PASI 75 response at Week 33 and were originally randomized to active therapy in period A were re-randomized in period C to receive 40 mg HUMIRA every other week or placebo for an additional 19 weeks. Across all treatment groups the mean baseline PASI score was 19 and the baseline Physician's Global Assessment score ranged from "moderate" (53%) to "severe" (41%) to "very severe" (6%). Study Ps-II evaluated 99 patients randomized to HUMIRA and 48 patients randomized to placebo with chronic plaque psoriasis with ≥10% BSA involvement and PASI ≥12. Patients received placebo, or an initial dose of 80 mg HUMIRA at Week 0 followed by 40 mg every other week starting at Week 1 for 16 weeks. Across all treatment groups the mean baseline PASI score was 21 and the baseline PGA score ranged from "moderate" (41%) to "severe" (51%) to "very severe" (8%). Studies Ps-I and II evaluated the proportion of patients who achieved "clear" or "minimal" disease on the 6-point PGA scale and the proportion of patients who achieved a reduction in PASI score of at least 75% (PASI 75) from baseline at Week 16 (see Table 13 and 14). Additionally, Study Ps-I evaluated the proportion of subjects who maintained a PGA of "clear" or "minimal" disease or a PASI 75 response after Week 33 and on or before Week 52.

The most serious adverse effects associated with adalimumab use are reports of serious infections, rare neurologic events, and malignancies. Adalimumab carries a black box warning stating a risk of infections that have been observed, specifically tuberculosis. Therapy should not be initiated in patients with active infections (chronic or localized). Development of new infections while receiving therapy with adalimumab necessitates close monitoring. Adalimumab should be discontinued if a patient develops a serious infection. Caution is needed when considering initiation of adalimumab in patients with a history of recurrent infection, in patients with underlying conditions predisposing to infections, or in patients geographically located where tuberculosis and histoplasmosis are widespread.

Drug Availability

Adalimumab (Humira[®]) is supplied in prefilled syringes for subcutaneous administration with the following packaging configurations:

- **HUMIRA Pen Carton:** a carton containing two alcohol preps and two dose trays with each dose tray consists of a single-use pen, containing a 1 mL prefilled glass syringe, providing 40 mg (0.8 mL) of Humira.
- **HUMIRA Pen – Crohn's Disease Starter Package:** a carton containing 6 alcohol preps and 6 dose trays with each dose tray consists of a single-use pen, containing a 1 mL prefilled glass syringe, providing 40 mg (0.8 mL) of Humira.
- **Prefilled Syringe Carton – 40 mg:** a carton containing two alcohol preps and two dose trays with each dose tray consists of a single-dose, 1 mL prefilled glass syringe, providing 40 mg (0.8 mL) of Humira.
- **Pediatric Prefilled Syringe Carton - 20 mg:** a carton containing two alcohol preps and two dose trays with each dose tray consists of a single-dose, 1 mL pre-filled glass syringe, providing 20 mg (0.4 mL) of Humira.

Coding/Billing Information

Note: This section is not in use.

References

1. Abbott Laboratories. Humira[®] (adalimumab) prescribing information, North Chicago, IL: Abbott Laboratories, February 2008.

2. American Thoracic Society, Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. *Am J Respir Crit Care Med*. 2000;161:S221–S247.
3. Callen JP, Krueger GG, Lebwohl M, McBurney EI, Mease P, Menter A, Paller AS, Pariser DM, Weinblatt M, Zimmerman G; AAD. AAD consensus statement on psoriasis therapies. *Am Acad Dermatol*. 2003 Nov;49(5):897-9.
4. Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Jan 2007*;132(1):52-65.
5. Felson DT, Anderson JJ, Boers M et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. *Arthritis Rheum*. 1993; 36:729-40.
6. Felson DT, Anderson JJ, Lange MLM et al. Should improvement in rheumatoid arthritis clinical trials be defined as fifty percent or seventy percent improvement in core set measures, rather than twenty percent. *Arthritis Rheum*. 1998; 41:1564-70.
7. Hanauer SB, Sandborn WJ, Rutgeerts P, et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the Classic-I trial. *Gastroenterology*, Feb 2006;130(2):323-33.
8. Heijde DV, Kivitz A, Schiff MH, et al. Efficacy and Safety of Adalimumab in Patients With Ankylosing Spondylitis. Results of a Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial. *Arthritis & Rheumatism*. Vol. 54, No. 7, July 2006, pp 2136–2146.
9. McEvoy GK, ed. AHFS 2009 Drug Information. Bethesda, MD: American Society of Health-Systems Pharmacists, Inc; 2009.
10. Pariser DM, Bagel J, Gelfand JM, Korman NJ, Ritchlin CT, Strober BE, Van Voorhees AS, Young M, Rittenberg S, Lebwohl MG, Horn EJ; National Psoriasis Foundation. National Psoriasis Foundation clinical consensus on disease severity. *Arch Dermatol*. 2007 Feb;143(2):239-42.
11. Rau R. Adalimumab (a fully human anti-tumor necrosis factor a monoclonal antibody) in the treatment of active rheumatoid arthritis: the initial results of five trials. *Ann Rheum Dis*. 2002; 61(Suppl II):ii70-3.
12. Saag KG, Teng GG, Patkar NM, et al. American College of Rheumatology 2008 Recommendations for the Use of Nonbiologic and Biologic Disease-Modifying Antirheumatic Drugs in Rheumatoid Arthritis. *Arthritis Rheum* 2008 Jun 15;59(6):762-84.
13. Sandborn WJ, Hanauer SB, Rutgeerts PJ, et al. Adalimumab for maintenance treatment of Crohn's disease: Results of the Classic II Trial. *Gut*. February 13, 2007.
14. Weinblatt ME, Keystone EC, Furst DE et al. Adalimumab, a fully human anti-tumor necrosis factor a monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate. The ARMADA trial. *Arthritis Rheum*. 2003; 48:35-45.

Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare Great-West Healthcare	7/15/2008	4062	Adalimumab (Humira®)

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