



CIGNA HEALTHCARE COVERAGE POSITION

Subject **Abatacept (Orencia®)**

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Hyperlink to Related Coverage Positions

Enbrel®
Humira®
Kineret®
Remicade®
Rituxan®

INSTRUCTIONS FOR USE

Coverage Positions are intended to supplement certain **standard** CIGNA HealthCare benefit plans. 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 Positions are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Position. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Positions. 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 Positions and; 4) the specific facts of the particular situation. Coverage Positions relate exclusively to the administration of health benefit plans. Coverage Positions are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2008 CIGNA

Coverage Position

CIGNA HealthCare covers abatacept (Orencia®) as medically necessary for the treatment of active rheumatoid arthritis (RA) in adults (≥18 years of age) OR polyarticular juvenile idiopathic arthritis (JIA) in patients ages 6–17 years of age AND when EITHER of the following indications is met:

- patients with the history of positive clinical response to abatacept therapy for RA/JIA condition
- patients with **NO** history of use of abatacept therapy:
 - **Initial authorization:** approval of 16 weeks when there is an inadequate response intolerance, or contraindication to at least **ONE** disease-modifying anti-rheumatic drugs (DMARDs) (i.e., Methotrexate (MTX) Azathioprine, gold, Hydroxychloroquine, Penicillamine, Sulfasalazine) **AND to ONE** tumor necrosis factor (TNF) antagonists [i.e. adalimumab (Humira®), etanercept (Enbrel®), infliximab (Remicade®)] as evidenced by documented disease progression based on the assessment of disease activity using **ANY** of the following:
 - elevation of ESR (> 28 mm/hr), or C-reactive protein (CRP) (2x the upper limit of normal)
 - 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 patient/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
- **Subsequent requests:** After 16 weeks, the approval of continuation of therapy for **ONE YEAR** when there is a clinical response to treatment and documented improvement indicated by using **ANY** of the following:
- ESR or CRP
 - 20% improvement according to ACR response criteria
 - HAQ-DI
 - VAS
 - Likert scales of global response to pain by the patient/doctor
 - GAS
 - CDAI
 - SDAI
 - DAS and DAS28 scores

CIGNA HealthCare does not cover abatacept (Orencia[®]) for the following indications because it is considered experimental, investigational or unproven (this list may not be all-inclusive).

- concomitant use with TNF antagonists for the treatment of RA
- concomitant use with anakinra (Kineret[®]) for the treatment of RA

General Background

FDA Approved Indications

Abatacept is a selective co-stimulation modulator indicated for the following:

- **Adult Rheumatoid Arthritis (RA)** - used alone or concomitantly with DMARDs other than TNF antagonists, for treatment of moderately to severely active RA in adults
- **Juvenile Idiopathic Arthritis (JIA)** - used alone or in combination with methotrexate, for treatment of moderately to severely active polyarticular juvenile idiopathic arthritis in pediatric patients six years of age and older.

In clinical trials, after administration of multiple doses of 10 mg/kg to patients with RA, the mean terminal half-life was 13.1 days, and the serum concentration appeared to reach a steady state by day 60. No systemic accumulation of abatacept occurred upon continued repeated treatment with 10 mg/kg at monthly intervals in patients with RA. Higher clearance of abatacept was reported with increasing body weight. Time to onset of clinical response was approximately two weeks from the initial dose. Three Phase III, double-blind, randomized, placebo-controlled trials evaluated the efficacy and safety of abatacept in patients with RA. Results showed that abatacept significantly reduces the signs and symptoms of RA among patients who had an inadequate response to disease-modifying anti-rheumatic drugs (DMARDs) or anti-tumor necrosis factor (TNF) therapy when compared to placebo. More than 2600 patients were studied in an extensive clinical trial program. The studies are summarized below.

A major goal in the treatment of RA is to improve signs and symptoms. According to the 2002 update on guidelines for management of RA developed by the American College of Rheumatology (ACR), the reduction of these symptoms can be clinically measured using the ACR response criteria. An ACR-20 response is defined as a 20% improvement in tender and swollen joint count as well as a 20% improvement in 3 of the following 5 parameters: patient's global assessment, physician's global assessment, and patient assessment of pain, degree of disability, and level of acute-phase reactant. Another goal is to reduce radiographic progression, which is slowing the rate of joint damage visible on Xray. 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. The most common measures used in the clinical settings include: Health

Assessment Questionnaire Disease Index (HAQ-DI), Visual Analogue scale (VAS), Likert scales of global response to pain by the patient/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, Elevation of ESR (> 28 mm/hr), or C-reactive protein (CRP).

Abatacept is a synthetic protein produced by recombinant deoxyribonucleic acid (DNA) technology that is indicated for treatment of rheumatoid arthritis (RA). Abatacept binds to CD80 and CD86 to block the interaction with CD28 required for full T lymphocyte (T cell) activation. Activated T cells have been found in the synovium of patients with RA and are implicated in the pathogenesis of the disease. Abatacept should not be given concomitantly with TNF antagonists.

Rheumatoid Arthritis (RA)

Abatacept in Inadequate Responders to Methotrexate (AIM)

A one-year, randomized, double-blind, placebo-controlled, multicenter Phase III trial compared abatacept in combination with methotrexate to methotrexate alone in a total of 652 patients with active RA who had inadequate response to methotrexate (MTX) treatment. Patients continued with their MTX therapy and were randomized in a 2:1 ratio to add a 30-minute intravenous infusion of either abatacept (approximately 10 mg/kg; n=433) or placebo (n=219) on days 1, 15, 29, and every 28 days thereafter; one additional DMARD was allowed at six months. Radiographs of hands and feet were performed at the start of the study and at one year or upon early termination, and scored using the Genant-modified Sharp scoring method, one of the study's co-primary objectives. Results showed that abatacept significantly inhibited the progression of structural damage compared to placebo. Of the 652, radiographs were collected from 391 of the 433 (92%) abatacept-treated subjects and 195 of the 219 (91%) placebo-treated subjects. Compared to placebo, abatacept-treated subjects demonstrated an inhibition of progression based on median change from baseline in structural damage as measured by joint erosion score (p=0.029), joint space narrowing score (p=0.009) and total score (p=0.012). Additionally, subjects receiving abatacept experienced fewer increases from baseline compared to the placebo arm in mean scores for joint erosion (0.63 vs. 1.14; p=0.008), joint space narrowing (0.58 vs. 1.18; p<0.001) and total score (1.21 vs. 2.32; p<0.001). A similar rate of adverse events were reported by both study groups.

Abatacept Trial in Treatment of Anti-TNF Inadequate Responders (ATTAIN)

A randomized, double-blind, phase III trial evaluated the efficacy and safety of abatacept in patients with active RA and an inadequate response to anti-TNF-alpha therapy. Before entering the study, patients discontinued anti-TNF-alpha therapy and were randomized 2:1 to receive abatacept or placebo on days 1, 15, and 29, and every 28 days thereafter for six months, in addition to at least one DMARD. Patients' responses were assessed according to the American College of Rheumatology (ACR) criteria (ACR20, ACR50, and ACR70), as defined by reductions of symptoms by 20%, 50%, and 70%, as well as Health Assessment Questionnaire (HAQ) responses and the Disease Activity Score 28 (DAS28). After six months, 50.4% of the patients had an ACR20 response in the abatacept group and 19.5% in the placebo group (p< 0.001). The abatacept group also fared better than the placebo group in the rates of ACR 50 (20.3% vs. 3.8%; p<0.001) and ACR 70 responses (10.2% vs. 1.5%, p= 0.003). At the end of the double-blind phase, 11.2% of patients had achieved remission according to DAS28 criteria; at the end of the extension phase, the remission rate according to this measure was 22.5%. According to the HAQ disability index, clinically meaningful improvement in physical function occurred in 47.3% of patients in the abatacept group and in 23.3% of patients in the placebo group (p<0.001). The most common adverse event reported was headache, with a rate of 79.5% in the treatment group and 71.4% in the placebo. Serious adverse events, consisting of infections and malignancies, were observed in 2.3% in each group.

Abatacept Study of Safety in Use with Other RA Therapies (ASSURE)

In a randomized study, the safety of abatacept in combination with biologic and nonbiologic DMARDs was compared to placebo. A total of 1441 patients, who were treated with either abatacept or placebo along with their DMARD medication, were randomized to take combination of abatacept and nonbiologic DMARD (n=856), abatacept and a biologic DMARD (n=103), placebo and a nonbiologic DMARD (n=418), or placebo and a biologic DMARD (n=64). Results showed similar rates of adverse events in the treatment and placebo groups, although the combination of abatacept and a biologic therapy was not tolerated as well as the combination with nonbiologic DMARDs. A greater number of adverse events occurred in the patients receiving abatacept and a biologic therapy (95.1%) compared to the other groups

(86–90%). Treatment-related adverse events occurred in 55.7% of abatacept-treated patients and 49.6% of placebo patients. Treatment-related serious adverse events occurred in 2.4% of abatacept patients and in 2.7% of those taking placebo. The most common adverse events were headache, nasopharyngitis, and nausea. No patients developed lymphoma, which has been the adverse event in patients treated with biologic DMARDs. Nine patients died in the study, and those deaths occurred in five of those in the abatacept group and four of those taking placebo. Four of the deaths in the abatacept group and two of those in the placebo group were probably cardiac-related as determined by autopsy.

Polyarticular Juvenile Idiopathic Arthritis (JIA)

The approval of this indication was based on the AWAKEN (Abatacept Withdrawal study to Assess efficacy and safety in Key Endpoints in juvenile idiopathic arthritis Not responding to current treatment) study, which evaluated the efficacy and safety of abatacept in patients six to 17 years of age with moderately to severely active polyarticular JIA who had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). The primary endpoint of the study was time to occurrence of disease flare. This trial was a three-part study which included: Period A - an open-label, lead-in period; Period B - double-blind randomized withdrawal phase; and Period C – an open-label extension. In period A, a total of 190 patients aged six to 17 years received abatacept 10 mg/kg intravenously on Days 1, 15, 29 and every month thereafter. Response was assessed utilizing the ACR Pediatric 30 definition of improvement, defined as greater than or equal to 30% improvement in at least three of the six JIA core set variables and greater than or equal to 30% worsening in not more than one of the JIA core set variables. In Period A of the study, abatacept demonstrated consistent improvement in ACR Pedi 30 with similar responses across all JIA subtypes. In patients who were inadequate responders to DMARDs including MTX and were new to biologic treatment, abatacept demonstrated meaningful ACR Pedi response rates with 76% of patients achieving an ACR Pedi 30 response rate, 60% achieving an ACR Pedi 50 response rate, 36 percent achieving an ACR Pedi 70 response rate and 17% achieving an ACR Pedi 90 response rate. In patients who received prior biological treatment, 38.6% achieved an ACR Pedi 30 response rate, 24.6% achieved an ACR Pedi 50 response rate, 10.5% achieved an ACR Pedi 70 response rate and 1.8% achieved an ACR Pedi 90 response rate. In Period B of the study, patients who completed Period A and achieved an ACR Pedi 30 response were eligible to enter this six-month, double-blind phase. Patients entering Period B (n=122) were randomized to remain on abatacept (n=60) or receive placebo (n=62) for six months. Results showed that time difference to occurrence of disease flare was statistically significant based on the log-rank test in patients treated with placebo compared with abatacept (p=0.0002). Patients treated with abatacept experienced significantly fewer disease flares compared to placebo-treated patients (20% vs. 53%, respectively, p< 0.001). In patients receiving abatacept treatment throughout all periods, the proportion of ACR Pedi 30, 50 and 70 responders remained consistent through one year.

Abatacept should not be used concurrently with TNF blockers and is not recommended for use with anakinra (Kineret®). Studies showed that patients receiving concurrent use of abatacept and a TNF blocker experienced more infections, including serious infections, compared to patients taking TNF blockers alone.

Since abatacept depresses the immune system, it reduces the body's ability to fight infection. Therefore, existing infections may worsen or new ones may develop. Abatacept should be used carefully in patients with a history of infection or underlying conditions which predispose them to infections. Warnings are also in place for patients testing positive for tuberculosis as well as patients with chronic obstructive pulmonary disease (COPD).

The most common side effects include headache, upper respiratory tract infections and nausea. Per abatacept's labeling, serious infections, including pneumonia and cellulitis, occurred in 3% of abatacept-treated patients. Infusion reactions such as dizziness, headache, hypotension or hypertension, wheezing, rash, and shortness of breath were reported in 9% of patients receiving abatacept versus 6% in patients treated with placebo.

Abatacept's dosage is based on a patient's weight. Patients weighing < 60 kg should receive a 500 mg dose; those weighing 60–100 kg a 750 mg dose; and patients weighing > 100 kg, a 1000 mg dose. Patients should receive an initial dose, a second dose two weeks later, a third dose two weeks after the

second, and then a dose every four weeks thereafter. All doses should be given as an intravenous infusion over a 30-minute period.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:

CPT®* Codes	Description

HCPCS Codes	Description

ICD-9-CM Diagnosis Codes	Description

Experimental/Investigational/Unproven/Not Covered:

CPT* Codes	Description

HCPCS Codes	Description

ICD-9-CM Diagnosis Codes	Description

*Current Procedural Terminology (CPT®) ©2005 American Medical Association: Chicago, IL.

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