



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.

Subject **Abatacept (Orencia®)**

Effective Date 7/15/2009
Next Review Date 7/15/2010
Coverage Policy Number 6112

Table of Contents

Coverage Policy	1
General Background	2
Coding/Billing Information	5
References	6
Policy History	7

Hyperlink to Related Coverage Policies

Enbrel®
Humira®
Kineret®
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 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 individuals ages 6–17 years of age when EITHER of the following indications is met:

- history of beneficial clinical response to abatacept 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) **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:
 - 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

Note: Where intravenous (IV) biologic response modifier therapy is required for Rheumatoid Arthritis (RA) treatment, there must be a failure, contraindication, or intolerance to infliximab (Remicade®) as the TNF Antagonist prior to use of abatacept (Orencia®).

Initial Authorizations: 16 weeks. 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 using ANY of the following:

- 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 score
- DAS28 score

CIGNA 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

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

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.

FDA Recommended Dosing

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.

The recommended dose of abatacept for patients 6 to 17 years of age with juvenile idiopathic arthritis who weigh less than 75 kg is 10 mg/kg calculated based on the patient's body weight at each administration. Pediatric patients weighing 75 kg or more should be administered abatacept following the adult dosing regimen, not to exceed a maximum dose of 1000 mg.

Abatacept is a synthetic protein produced by recombinant deoxyribonucleic acid (DNA) technology that is indicated for treatment of rheumatoid arthritis (RA). Abatacept should not be given concomitantly with TNF antagonists.

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 U.S. Food and Drug Administration (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.

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.

Clinical Efficacy

- **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.

Precautions/Warnings

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).

Drug Availability

Abatacept for intravenous infusion is supplied as an individually packaged, single-use vial providing 250 mg of abatacept in a 15-mL vial.

Coding/Billing Information

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

Covered when medically necessary:

HCPCS Codes	Description
J0129	Injection, abatacept, 10 mg

ICD-9-CM Diagnosis Codes	Description

714.0	Rheumatoid arthritis
714.30- 714.33	Juvenile chronic polyarthritis

References

1. Bristol-Myers Squibb Company. Orenzia[®] (abatacept) Product Information. Princeton, NJ: Bristol-Myers Squibb Company. April 2008.
2. Genant H, Peterfy C, Pairea, S. et al. Abatacept significantly inhibits structural damage progression assessed by the Genant-Modified Sharp Scoring System in rheumatoid arthritis patients with inadequate methotrexate responses. Abstract available at: <http://www.hopkins-arthritis.som.jhmi.edu/edu/eular2005/ra-treatments-ctla4.html>. Accessed on February 22, 2006.
3. Genovese MC, Becker JC, Schiff M, et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. *N Engl J Med*. 2005;353(11):1114-23.
4. Kremer JM, Genant HK, Moreland LW. et al. Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. *Ann Intern Med*. 2006 Jun 20;144(12):865-76.
5. Mobsy's Drug Consult. Drug News: New drug approval updates 2005. Available at: <http://www.mosbysdrugconsult.com/DrugConsult/newapp2005.html>. Accessed on February 20, 2006.
6. 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.
7. Weinblatt M, Combe B, White A, Aranda R, Becker J, Keystone, E. Safety of abatacept in patients with active rheumatoid arthritis receiving background non-biologic and biologic DMARDs: 1- year results of the ASSURE Trial. Abstract available at: <http://www.hopkins-arthritis.som.jhmi.edu/edu/eular2005/ra-treatments-ctla4>.

Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare Great-West Healthcare	7/15/2008	6112	Abatacept (Orencia®)

“CIGNA” and the “Tree of Life” logo are registered service marks of CIGNA Intellectual Property, Inc., licensed for use by CIGNA Corporation and its operating subsidiaries. All products and services are provided exclusively by such operating subsidiaries and not by CIGNA Corporation. Such operating subsidiaries include Connecticut General Life Insurance Company, CIGNA Behavioral Health, Inc., Intracorp, and HMO or service company subsidiaries of CIGNA Health Corporation and CIGNA Dental Health, Inc. In Arizona, HMO plans are offered by CIGNA HealthCare of Arizona, Inc. In California, HMO plans are offered by CIGNA HealthCare of California, Inc. and Great-West Healthcare of California, Inc. In Connecticut, HMO plans are offered by CIGNA HealthCare of Connecticut, Inc. In North Carolina, HMO plans are offered by CIGNA HealthCare of North Carolina, Inc. In Virginia, HMO plans are offered by CIGNA HealthCare Mid-Atlantic, Inc. All other medical plans in these states are insured or administered by Connecticut General Life Insurance Company.

Connecticut General Life Insurance Company has acquired the business of Great-West Healthcare from Great-West Life & Annuity Insurance Company (GWLA). Certain products continue to be provided by GWLA (Life, Accident and Disability, and Excess Loss). GWLA is not licensed to do business in New York. In New York, these products are sold by GWLA’s subsidiary, First Great-West Life & Annuity Insurance Company, White Plains, N.Y.