

<b>Subject: Abatacept - ORENCIA®</b>	
<input type="checkbox"/> Original	<b>Original Committee Approval: March 10, 2006</b>
<input checked="" type="checkbox"/> Revised	<b>Last Committee Approval: December 3, 2008</b>
	<b>Last Review: June 8, 2007</b>

## 1. Background:

Rheumatoid arthritis (RA) is a chronic, progressive, inflammatory, autoimmune disease affecting about 1% of the US adult population and occurs approximately 3 times more frequently in women than in men.<sup>1</sup> Almost 80% of RA cases occur in patients between 35 and 50 years of age<sup>2</sup>; usually a time of peak social productivity. The disease is characterized by persistent inflammation of the synovium, cartilage loss, and bone erosion in peripheral joints, usually in a symmetric fashion. Research has shown that joint damage occurs within the first 2 years of symptoms and diagnosis and progresses rapidly if not treated.<sup>3,4,5</sup> Although RA primarily affects the joints, it is a systemic disease and does cause systemic and extra-articular clinical features (e.g., fever, fatigue, anorexia, weight loss, and anemia). Patients with RA also have greater mortality than the general population.

RA immunopathology involves multiple cell types and signaling mechanisms (cytokines). Recent evidence suggests that T-cells substantially contribute to RA immunopathology, as evidenced by their presence in RA synovial specimens.<sup>6</sup> In order for T-cells to become fully activated and to contribute to the disease pathogenesis, they require two signals: one from antigen-specific T-cell receptors plus one via a non-antigen-specific costimulatory receptor, typically CD28. CD28 is expressed on T-cells and binds to both CD80 (B7-1) and CD86 (B7-2) on activated antigen-presenting cells.

Abatacept (CTLA-4Ig) is a first-in-class selective costimulation modulator. CTLA-4Ig is a soluble fusion protein comprised of the ligand-binding domain of CTLA-4 and the tail end of human immunoglobulin.<sup>7</sup> CTLA-4 is normally expressed on the cell surface of activated T-cells and on regulatory T-cells. It binds CD80 and CD86 with approximately 100-fold higher affinity than CD28.<sup>8</sup> This binding blocks full T-cell activation and proliferation and inhibits the production of various cytokines associated with inflammation including TNF-alpha, interferon gamma, and interleukin-2. It is unknown if this cytokine modulation contributes to the drug's efficacy in RA.

Labeling for Orencia® indicates clinical data from five pivotal, randomized, double-blind, placebo-controlled studies provided the evidence for its efficacy, safety, and approval for the treatment of adult patients with RA. Only one of these studies (Study 4) is currently fully published.<sup>8</sup> In Study 4, the efficacy and safety of abatacept was assessed in patients with an inadequate response to a TNFI; the TNFI was discontinued prior to randomization, but concurrent use of other disease-modifying antirheumatic drugs (DMARDs) was permitted. The proportion of patients achieving an ACR 20, 50, or 70 response at 6-months was significantly

greater in the group receiving abatacept + DMARDs compared with the group receiving placebo + DMARDs (all  $P < .01$ ). In addition, a greater proportion of patients receiving abatacept + DMARDs achieved a clinically and statistically significant improvement in Health Assessment Questionnaire (HAQ) disability index scoring compared with the group receiving placebo + DMARDs ( $P < .001$ ). Abatacept was also well tolerated; headache was the only adverse event that occurred more frequently in the group receiving abatacept compared with control. Other fully published clinical trials for abatacept include one 6-month phase 2 study<sup>9</sup>, its 6-month extension<sup>10</sup>, and a pilot study<sup>11</sup>.

In total (published and unpublished) clinical trial evidence consistently indicates the agent has clinical benefit for treatment-refractory RA patients (in terms of ACR response, improvement in HAQ disability index, and radiographic response) at least in combination with stable doses of concurrent DMARDs. There are no head-to-head comparative clinical studies with biologic DMARDs, and because many of the phase 3 clinical trials are not fully published, relative efficacy and safety compared to biologic DMARDs cannot be established at this time. Current safety data indicates some issues: a higher incidence of serious infections when used in combination with TNFIs and a greater incidence of adverse effects, including worsening of respiratory status in patients with concurrent COPD. Availability of longer-term (>1 year) safety data is limited; while such evidence for the newer biologic DMARDs consists of substantial patient-years.

## **2. Indications/Criteria:**

The use of abatacept may be considered medically necessary in patients (age  $\geq 18$  years) meeting all of the following criteria:

- Diagnosis of moderate to severe RA (Class II-IV) as defined by American College of Rheumatology.
- Patient is on stable doses of DMARDs.
- Previous trial and failure with one formulary TNF-alpha inhibitor (TNFI) (etanercept [Enbrel<sup>®</sup>] or adalimumab [Humira<sup>™</sup>]), unless contraindications to use of a TNFI are present.
- Patient's therapeutic plan does not include concurrent therapy with a TNFI (e.g., adalimumab [Humira<sup>™</sup>], etanercept [Enbrel<sup>®</sup>] or infliximab [Remicade<sup>®</sup>]), anakinra, (Kinerep<sup>™</sup>) or rituximab (Rituxan<sup>™</sup>).
- Dosing should not exceed 1000 mg every 2 weeks x 3 doses (initial load), then 1000 mg every 4 weeks.

**Retreatment Criteria:**

- After the initial 3 infusions, retreatment with abatacept (Orencia®) may be approved at a maximum of 13 infusions in a 12 month time period based on the following criteria:
  - \* An improvement in any 1 of the following American College of Rheumatology assessment components for improvement:
    - painful joint count
    - swollen joint count
    - patient pain assessment
    - patient global assessment
    - physician global assessment
    - patient self-assessed disability
    - acute phase reactants (ESR or CRP)

The use of abatacept will be considered investigational for the treatment of patients with other types of arthropathies and/or other pathological indications.

**3. Limitations/Exclusions:**

Healthy Options	None; pre-authorization required
Medicare Advantage	None; pre-authorization required
Basic Health Plan	None; pre-authorization required

**4. Required Review and Approvals:**

Abatacept (Orencia®) infusions require prior authorization by the CHP Medical Director or his/her designee. Each authorization period will be for six months.

**5. References:**

\*\*\*Attn: Eric 9-18-08

<sup>1</sup> American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis: 2002 update. *Arthritis Rheum.* 2002;46:328-346.

<sup>2</sup> Kavanaugh AF, Lipsky PE. Rheumatoid arthritis. In: Rich RR, Fleisher TA, Schwartz B et al, eds. *Clinical Immunology: Principles and Practice*. St. Louis, MO: Mosby-Year Book, 1996:1093-1116.

<sup>3</sup> van der Heijde DMFM, van Leeuwen MA, van Riel PLCM, et al. Biannual radiographic assessments of hands and feet in a three-year prospective followup of patients with early rheumatoid arthritis. *Arthritis Rheum.* 1992;35:26-34.

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- <sup>4</sup> Plant MJ, Saklatvala J, Borg AA, Jones PW, Dawes PT. Measurement and prediction of radiological progression in early rheumatoid arthritis. *J Rheumatol.* 1994;21:1808-1813.
- <sup>5</sup> van der Heijde DM. Joint erosions and the patient with early rheumatoid arthritis. *Br J Rheumatol.* 1995;34(suppl 2):74-78.
- <sup>6</sup> Cron RQ. A signal achievement in the treatment of arthritis. *Arthritis Rheum.* 2005;52(8):2229-2232.
- <sup>7</sup> Orencia<sup>®</sup> (abatacept) prescribing information. Bristol-Myers Squibb Company; Princeton, NJ; December 2005.
- <sup>8</sup> Genovese MC, Becker J-C, Schiff M, et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor- $\alpha$  inhibition. *N Engl J Med.* 2005;353:1114-1123.
- <sup>9</sup> Kremer JM, Westhovens R, Leon M, et al. Treatment of rheumatoid arthritis by selective inhibition of T-cell activation with fusion protein CTLA4Ig. *N Engl J Med.* 2003;349:1907-1915.
- <sup>10</sup> Kremer JM, Dougados M, Emery P, et al. Treatment of rheumatoid arthritis with the selective costimulation modulator abatacept. Twelve-month results of a phase IIb, double-blind, randomized, placebo-controlled trial. *Arthritis Rheum.* 2005;52(8):2263-2271.
- <sup>11</sup> Moreland LW, Alten R, Van den Bosch F, et al. Costimulatory blockade in patients with rheumatoid arthritis. A pilot, dose-finding, double-blind, placebo-controlled clinical trial evaluating CTLA-4Ig and LEA29Y eighty-five days after the first infusion. *Arthritis Rheum.* 2002;46(6):1470-1479.