

New Drug Bulletin:
abatacept (Orencia® - Bristol-Myers Squibb Company)

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Abatacept (Orencia®), approved on December 23, 2005, is the first in a new class of drugs known as costimulation modulators. Abatacept exerts its effects by interacting with T lymphocytes, also called T-cells. T-cells likely play a major role in the pathogenesis of rheumatoid arthritis (RA). T-cells are found in the synovium of patients afflicted with RA. Pathogenic T-cells taken from the synovium of patients with RA induce arthritis when injected into immunodeficient mice. CD28 is a cell surface antigen found on T-cells. CD28 helps activate T-cells by binding to CD80 or CD86 ligands expressed on antigen presenting cells, activation that is blocked by abatacept binding to CD28.

Abatacept has a terminal half life of 13 hours following multiple infusions. Few data are available describing the renal or hepatic clearance of abatacept.

Five controlled studies reported in the product labeling demonstrated the clinical response of active RA treated with abatacept. Enrolled adults had active RA based on the American College of Rheumatology (ACR) criteria. Three fundamental assessments were used to evaluate the improvement in RA symptoms: ACR response rate, radiographic evaluation, and physical function response. The achievement of an ACR 70 response for a continuous 6 month period was considered to be a major clinical response. (Major clinical response is defined as a 70% reduction in the number of swollen and tender joints and a reduction in three of five parameters assessing pain, disease state, and biological markers). Patients obtained a major clinical response in only one of five clinical studies. In this study, 14% of patients with an inadequate response to methotrexate (MTX) had a major clinical response when abatacept was added to MTX therapy, compared to 27% of placebo-treated patients, $p < 0.001$. Positive clinical outcomes in ACR 20, ACR 50 and ACR 70 were obtained to some degree in all five clinical studies.

The most common adverse effects reported with abatacept included headache, upper respiratory tract infection, nasopharyngitis and nausea. Infection was the most frequent cause of treatment discontinuation in clinical studies. Because abatacept increases the risk for general infection, evaluate patients for chronic, latent or localized infections, including a history of recurrent infections and tuberculosis. Patients with chronic obstructive pulmonary disease (COPD) receiving abatacept had more COPD exacerbations than patients receiving placebo.

An increased occurrence of malignant lymphomas and mammary gland tumors was noted in studies that evaluated abatacept in mice, but the significance in humans is unknown. The occurrence of malignancies in patients treated with abatacept (1.3%) was similar to placebo (1.1%). The presence of binding antibodies to the abatacept molecule was detected in 34 of 1993 patients evaluated, though this was not correlated with efficacy or toxicity.

Special populations have few trial data with abatacept. No data are available in children or pregnant women with RA. Abatacept did not cause teratogenic effects when tested in mice, but was shown to cross the placenta. No differences were appreciated when use of

abatacept in a small number of geriatric patients compared to use in younger patients. Geriatric patients may be more susceptible to infections and malignancies, so use caution when administering abatacept to this population.

No formal drug interaction studies are available for abatacept. Abatacept clearance was not affected when given concomitantly with MTX, NSAIDs, corticosteroids, and tumor necrosis factor (TNF) inhibitors in clinical studies. The concurrent administration of abatacept with TNF inhibitors, anakinra or live vaccines is not recommended because of the risk for serious infections. The efficacy of all vaccines may be compromised if administered during abatacept therapy.

Abatacept dosing depends on the total body weight of each patient (see Table). Administer the first abatacept intravenous infusion over 30 minutes. Give the second dose two weeks after the first, and the third at four weeks after the initial infusion. Maintenance doses are infused every four weeks after that. Patients in open-label studies have received abatacept therapy for up to 3 years.

Abatacept is available in 250 mg single-use vials that should be refrigerated and protected from light. Reconstitute vials with 10 mL of sterile water using only silicone-free syringes. Gently swirl the solution and avoid prolonged agitation or shaking. The solution must be further diluted with 100 mL of 0.9% sodium chloride injection prior to infusion. The reconstituted solution may be refrigerated or stored at room temperature but must be infused within 24 hours of reconstitution.

Average wholesale price is not currently available for abatacept.

In summary, placebo-controlled trials indicate that abatacept is an effective and safe second-line treatment for RA.

References:

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