

Orencia® Approved for Rheumatoid Arthritis

The following is a brief summary of a newly approved drug. The complete prescribing information should be consulted before use in a specific patient.

Orencia® (abatacept) was approved at the end of December 2005 as a second-line treatment for moderately to severely active rheumatoid arthritis (RA) in adults. It will be used to reduce the signs and symptoms of RA, slow the structural damage associated with the disease, and improve physical function in patients who have had an inadequate response to methotrexate, tumor necrosis-factor (TNF) antagonists, or other disease-modifying antirheumatic drugs (DMARDs). Orencia may be used alone or with a DMARD—other than a TNF antagonist. Orencia may not be used with anakinra (Kineret), an interleukin-1 receptor antagonist.

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Mechanism of Action: Abatacept is a protein that is produced by recombinant DNA technology. It combines part of the T-lymphocyte-associated antigen 4 (CTLA-4) with part of human immunoglobulin G1 (IgG1), and acts as a selective costimulation modulator. It inhibits T cell activation by binding to CD80 and CD86, thereby blocking interaction with CD28. This disrupts the pathway of a signal necessary for the full activation of T cells, which are believed to be involved in the pathogenesis of rheumatoid arthritis.

Contraindications, Warnings, & Precautions: In clinical trials, patients who received both Orencia and a TNF antagonist experienced more infections, and more serious infections, as compared to patients treated with only TNF antagonists. These trials also failed to demonstrate any benefit in combining Orencia with TNF antagonist therapy; therefore, concurrent use of these agents is not recommended. Use of Orencia in patients with Chronic Obstructive Pulmonary Disease (COPD) may result in a higher frequency of adverse events and requires both caution and diligent patient monitoring for worsening respiratory status. Orencia may blunt the effectiveness of some immunizations, due to its mechanism of action.

Infusion Reactions: In trials, about 9% of patients experienced an infusion-related reaction within 1 hour of the start of the infusion. Of 2688 patients, 2 cases of anaphylactoid reactions were reported. Appropriate medical support should be available during all Orencia infusions.

Infection Screening: As with certain other immunomodulatory therapies, candidates for Orencia therapy should be screened for latent tuberculosis infection prior to starting treatment, and patients who test positive must be treated for tuberculosis prior to starting therapy with Orencia. Caution should also be used in patients with a history of recurrent infections or conditions pre-disposing them to infection.

Other Adverse Effects: The most common adverse events (occurring in $\geq 10\%$ of patients) experienced during clinical trials were headache, upper respiratory infection, nasopharyngitis or nausea. Serious infections, including pneumonia and cellulitis, were reported in 3% of abatacept-treated patients.

Dosing and Administration: Patients receive an initial dose, a second dose 2 weeks later, a third dose after another 2 weeks, and then a dose every 4 weeks thereafter. Doses of 500-1000 mg are mixed in a final total volume of 100 ml in Normal Saline and are given as a 30-minute intravenous infusion through a 0.2-1.2 micron, low protein-binding filter. Orencia is dosed by body weight as follows:

- < 60 kg: 500 mg dose (2 vials)
- 60-100 kg: 750 mg dose (3 vials)
- >100 kg: 1000 mg dose (4 vials)

Product Information: Orencia is a sterile white lyophilized powder for parenteral administration, and is stored under refrigeration before use. Each vial contains 250 mg of active drug. Refer to the product's specific preparation instructions for complete details. The powder is reconstituted with 10 mL sterile water, using a vented needle in order to dissipate any foam that occurs. It should be used within 24 hours after mixing. **A silicone-free syringe is required for handling the drug solution.** Exposure to silicone at any time may produce translucent particles and render the drug solution unusable. Special syringes are supplied with the product, and the manufacturer also offers a telephone number for ordering replacement syringes in case one is dropped or contaminated. Expected commercial availability: February 2006.

Reference: official prescribing information for Orencia®

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Longer Needles Required for Injection in Obese Patients

Many medications are designed to be introduced into a major muscle, such as the anterolateral thigh. When a drug intended for intramuscular (IM) use is injected too shallowly, such as into a subcutaneous fat layer, some or all of the medication's effectiveness may be lost. Subcutaneous tissue has fewer blood vessels than muscle, and is less effective at distributing medications. In addition, poorly aimed injections may result in sterile abscesses, granuloma, or local irritation in the tissue.

A recent small study of 50 patients (equally divided between men and women) showed an overall failure rate of 68% in getting an injection into the intended muscle in the upper quadrant of the buttocks. Among the women, 92% of the injections missed the target, and 44% were missed in the male patients.

Clinicians should consider each patient's individual characteristics when choosing a needle length for IM injections, and should not assume that a 'standard' needle will be appropriate for all patients. Health care professionals should especially consider using a longer needle when administering IM injections to overweight patients.

The Immunization Action Coalition (IAC) provides additional information about immunization-related injections on their two websites: www.immunize.org and www.vaccineinformation.org. The IAC has a chart of adult vaccination doses, sites and needle sizes available for download from their catalog at: <http://www.immunize.org/catg.d/p3084.pdf>

Infusion Partners maintains a chart of suggested needle sizes for injections in adults and children, for both intramuscular and subcutaneous injections. Copies are available upon request through the local Infusion Partners center, or by sending your request to Cathy Johnson at the Infusion Partners corporate office: cjohnson@infusionpartners.com. Please state your name, your organization, and the document you are requesting.



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when it comes to needles
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Update on Tysabri (natalizumab)

A supplemental Biologics License Application (sBLA) for Tysabri for the treatment of multiple sclerosis (MS) has been accepted and designated for priority review by the U.S. Food and Drug Administration (FDA). Priority review is granted for products that are considered to be potentially significant therapeutic advances over existing therapies. The sBLA was filed in late September 2005, and action by the FDA is anticipated by April 2006.

The new sBLA includes final 2-year data from the phase III AFFIRM monotherapy trial and the SENTINEL add-on trial with AVONEX in MS. The application also includes an integrated safety assessment of patients treated with Tysabri in clinical trials, a revised label, and a risk management plan.

Tysabri was originally approved by the FDA in November 2004, on a "fast-track" basis. This accelerated approval process is used for drugs that appear to offer a significant advance in health care. However, drugs approved on a "fast-track" schedule only have a limited set of safety and efficacy data because the clinical trials are not yet concluded. In the case of Tysabri, the drug was voluntarily suspended from the market in February 2005 after three isolated reports of progressive multifocal leukoencephalopathy (PML) occurred. PML is a rare and fatal disease of the central nervous system.

A comprehensive safety review of more than 3000 patients has now been conducted by the Biogen Idec and Elan drug companies, in collaboration with leading experts in PML and neurology. No new confirmed cases of PML were discovered. A spokesman for Elan stated recently that, "We will continue to work closely with the FDA as they review the filing so that Tysabri can be made available with an appropriate benefit-risk profile".

In a separate study examining the use of Tysabri in Crohn's Disease, the final study results appear to be inconclusive. Patients who responded early in the study achieved some clinical benefit, while patients who did not respond early showed no improvement even after the maintenance phase of the trial. Tysabri is not currently marketed in the U.S. for treatment of Crohn's Disease.



*Research into the
safety and efficacy of
Tysabri continues*