Adalimumab (Humira™)

**Manufacturer:** Abbott Laboratories, North Chicago, IL

**Indication:** Treatment of rheumatoid arthritis (RA)

**Drug Class:** Adalimumab is a recombinant human immunoglobulin G (IgG1) monoclonal antibody that is specific for human tumor necrosis factor (TNF). It was created using phage-display technology, resulting in an antibody with human-derived heavy chain and light chain variable regions and human IgG1-k constant regions. Adalimumab is produced by recombinant DNA technology in a mammalian cell expression system and is purified by a process that includes specific steps of viral inactivation and removal. Consisting of 1,330 amino acids, it has a molecular weight of approximately 148 kd.

**Uniqueness of Drug:** Adalimumab is the first human monoclonal antibody approved for reducing the signs and symptoms of RA, and for inhibiting the progression of structural damage, in adults with moderately to severely active RA who have not responded adequately to one or more traditional disease-modifying antirheumatic drugs (DMARDs).

**Boxed Warning—Risk of Infections:** Cases of tuberculosis (frequently disseminated or extrapulmonary at clinical presentation) have been observed in patients receiving adalimumab. A tuberculin skin test should be used to evaluate patients for latent tuberculosis infection, which, if present, should be treated before adalimumab therapy is initiated.

**Warnings**

**Infections**

Serious infections and sepsis, sometimes resulting in fatalities, have been reported with the use of TNF-blocking agents, including adalimumab. Many of these infections have occurred in patients receiving concomitant immunosuppressive therapies that can predispose them to tuberculosis in addition to their existing RA. Invasive opportunistic fungal infections have also been observed in patients receiving TNF-blocking agents, including adalimumab.

Adalimumab therapy should not be initiated in patients with any active chronic or localized infections. If new infections develop during therapy, close monitoring is essential. If serious infections develop, adalimumab administration should be discontinued. Physicians should exercise caution when considering the use of adalimumab in patients with a history of recurrent infections or underlying conditions, which may predispose them to infections, or in patients who have resided in regions where tuberculosis and histoplasmosis are endemic. Physicians should carefully consider the benefits and risks of adalimumab treatment before initiating therapy.

**Demyelinating Disease**

The use of TNF-blocking agents, including adalimumab, has been associated with rare cases of exacerbation of clinical symptoms and with radiographic evidence of demyelinating disease. Prescribers should use caution in considering adalimumab for patients with pre-existing or recent-onset central nervous system demyelinating disorders.

**Malignancy**

Lymphomas have been observed in patients taking TNF-blocking agents, including adalimumab. In clinical trials, the incidence of lymphoma was higher than the expected rate in patients who had taken adalimumab than in the general population. Patients with RA, particularly those with highly active disease, may be at a higher risk (up to several-fold) for lymphoma, although the role of TNF blockers in the development of malignancy is not known.

**Precautions:** Allergic reactions have been observed in approximately 1% of patients receiving adalimumab. If an anaphylactic reaction or other serious allergic reactions occur, administration of adalimumab should be discontinued immediately and appropriate therapy should be initiated.

The first injection should be performed under the supervision of a qualified health care professional. If patients or caregivers plan to administer adalimumab, they should be instructed in injection techniques; their ability to inject the drug as a subcutaneous (SQ) dose should also be assessed to ensure proper administration technique.

It is possible that TNF-blocking agents, including adalimumab, might affect host defenses against infections and malignancies because TNF mediates inflammation and modulates cellular immune responses.

As observed with TNF-blocking agents, adalimumab has been associated with tuberculosis in clinical trials. Tuberculosis was observed with all dosages, but the incidence of tuberculosis reactivations was especially greater when the adalimumab doses were higher than the recommended dose. All patients recovered from tuberculosis after standard antimicrobial therapy. No deaths were attributable to tuberculosis during the clinical trials.

**Dosage:** The recommended dose of adalimumab for adult patients with RA is 40 mg, administered every other week as an SQ injection. Methotrexate, glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, or other DMARDs may be continued during treatment with adalimumab. Some patients who are not taking concomitant methotrexate may derive additional benefit from increasing the dosing frequency of adalimumab to 40 mg every week.

Adalimumab is intended for use under the guidance and supervision of a physician. Patients may self-inject adalimumab if their physician determines that it is appropriate and with medical follow-up, as necessary, after proper training in injection technique.

The adalimumab solution in the syringe and in the vial should be carefully inspected visually for particulate matter and discoloration before SQ administration. If particulates and...
discolorations are noted, the product should not be used.

**P&T Committee Considerations:** Adalimumab has been approved to reduce the signs and symptoms of RA, and to inhibit the process of structural damage, in adult patients with moderately to severely active RA who have not benefited sufficiently after treatment with one or more DMARDS. Adalimumab offers convenience as an every-other-week SQ injection. A specially designed prefilled syringe will be available, making the self-injection process easier for patients whose hands have been damaged or deformed by the disease.

Adalimumab can be used alone or in combination with methotrexate. The efficacy of adalimumab was assessed by evaluating improvement in RA signs and symptoms response scores and in inhibition of the progression of structural damage, as measured by bone changes in x-ray films. Twenty-two percent (14 of 63 patients) experienced improvement in signs and symptoms of RA as early as one week after the beginning of treatment.

Adalimumab must be used with caution. The most serious adverse drug events associated with it are infections, neurological effects, and certain malignancies of the lymphoid system. Compared with the general population, patients with RA, particularly those with active disease, appear to be at greater risk for the development of lymphomas. Patients with RA should discuss therapy options with their health care providers.

Adalimumab is appropriate for inclusion on the formulary, but prescribers should first gain a thorough awareness of the patient’s general health before initiating therapy.

The manufacturer’s wholesale price of adalimumab is $13,500 for a year’s treatment, about the same as for etanercept (Enbrel®, Immunex, Wyeth-Ayerst) and infliximab (Remicade®, Centocor); both cost upwards of $13,940 a year to administer. The list price from the manufacturer or the wholesale acquisition cost (WAC) for 2- to 40-kg prefilled syringes of adalimumab plus two alcohol preparations is $1,045.28.

**Alefacept (Amevive®)**

**Manufacturer:** Biogen, Inc., Cambridge, MA

**Indication:** Alefacept is indicated for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy.

**Drug Class:** Alefacept is an immunosuppressive, dimeric, fusion protein that consists of the extracellular CD2-binding portion of the human leukocyte function antigen-3 (LFA-3) linked to the Fc (hinge, CH2 and CH3 domains) portion of human IgG1. Alefacept is produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian cell expression system. The drug’s molecular weight is 91.4 kd.

**Uniqueness of Drug:** Alefacept therapy offers the first biological treatment approved for adults with moderate to severe chronic plaque psoriasis.

**Warnings**

**Lymphopenia**

Alefacept induces dose-dependent reductions in circulating CD4+ and CD8+ T-lymphocyte counts. A course of alefacept therapy should not be initiated in patients with CD4+ T-lymphocyte counts below normal. The CD4+ T-lymphocyte counts of patients receiving alefacept should be monitored weekly throughout the course of the 12-week dosing regimen. Dosing should be withheld if CD4+ T-lymphocyte counts are below 250 cells per microliter (cells/µl), and therapy should be discontinued if the counts remain below 250 cells/µl for one month.

**Malignancies**

In clinical studies, patients who received alefacept therapy appeared to be at risk for the development of malignancies. In preclinical studies, B-cell hyperplasia occurred in animals, with a lymphoma developing in one animal. Alefacept should not be administered to patients with a history of systemic malignancy. Prescribers should exercise caution when considering the use of alefacept in patients at high risk for malignancy. If a malignancy develops, alefacept administration should be discontinued.

**Infections**

Alefacept is an immunosuppressive agent and thus has the potential to increase the risk of infection and to reactivate latent, chronic infections. It should not be administered to patients with clinically serious infections. Prescribers should exercise caution when considering the use of alefacept in patients with chronic infections or a history of recurrent infection.

Patients should be monitored for signs and symptoms of infection during or after a course of alefacept. New infections should be closely monitored. If a serious infection develops, alefacept therapy should be discontinued.

**Precautions**

**Effects on the Immune System**

Patients receiving other immunosuppressive agents or phototherapy should not receive concurrent therapy with alefacept because of the possibility of excessive immunosuppression. The length of the period before one considers starting other immunosuppressive therapy after treatment with alefacept has not been evaluated.

In a study of 46 patients with chronic plaque psoriasis, the ability to mount immunity to tetanus toxoid (recall antigen) and an experimental neoantigen was preserved in those patients who were undergoing alefacept therapy.

**Allergic Reactions**

Hypersensitivity reactions (urticaria, angioedema) were associated with the administration of alefacept. If an anaphylactic reaction or other serious allergic reaction occurs, administration of alefacept should be discontinued immediately and appropriate therapy should be initiated.

**Information for Patients**

Patients should be informed that:

- regular monitoring of white blood cell (lymphocyte) counts is required during therapy.
- alefacept must be administered under the supervision of a physician.
- alefacept therapy results in a reduced lymphocyte count, which might increase the risk of infection or malignancy.

Women of childbearing age make up a considerable segment of the patient population that is affected by psoriasis. Because the effect of alefacept on pregnancy, fetal development, and immune system development is unknown, health care
providers are encouraged to enroll patients who are currently taking alefacept and who become pregnant into the Biogen Pregnancy Registry. Women should also be advised to notify their physicians if they become pregnant while taking alefacept (or within eight weeks of discontinuing alefacept) and should be encouraged to enroll in the Pregnancy Registry.

CD4+ T-lymphocyte counts should be monitored weekly during the 12-week dosing period and should be used to guide dosing. Patients should have normal CD4+ T-lymphocyte counts before an initial or a subsequent course of treatment with alefacept. Dosing should be withheld if CD4+ T-lymphocyte counts are below 250 cells/µl. Alefacept should be discontinued if CD4+ T-lymphocyte counts remain below 250 cells/µl for one month.

Dosage: Alefacept should be used only under the guidance and supervision of a physician. The recommended dose is 7.5 mg, given once weekly as an intravenous bolus or 15 mg given once weekly as an intramuscular injection. The recommended regimen is a course of 12 weekly injections. Re-treatment with an additional 12-week course may be initiated if CD4+ T-lymphocyte counts are within the normal range and a minimum of a 12-week interval has passed since the previous course of treatment. Data on re-treatment beyond two cycles are limited.

The CD4+ T lymphocyte counts of patients receiving alefacept should be monitored weekly before dosing has begun and throughout the course of the 12-week regimen. As stated previously in this article, dosing should be withheld if these counts are below 250 cells/µl and the drug should be discontinued if the counts remain below 250 cells/µl for one month.

P&T Committee Considerations: Psoriasis, which stems from a rapid runaway autoimmune response in the skin, causes skin itching, redness, flaking, pain, and cracking in about 2% of the population, or 5.5 million people, each year. The availability of alefacept may improve treatment of the disease, which currently relies on broad-based anti-inflammation techniques with limited effectiveness or with side effects.

Alefacept is the first drug from the biotechnology industry to treat this debilitating skin ailment. Approximately 1.5 million American adults have moderate to severe psoriasis. Alefacept directly affects psoriasis-related inflammation through a specific immune-blocking action without undercutting the rest of the immune system and its ability to fight infection. It relieves symptoms during treatment and may spur remission. A pooled safety profile of alefacept, based on the results of three placebo-controlled trials that included 1,289 patients with chronic plaque psoriasis, showed that alefacept was well tolerated in psoriasis patients and had a safety and tolerability profile comparable to that of placebo. Nevertheless, the label’s warnings and precautions suggest that alefacept should be used with caution and that methotrexate should be the initial treatment of psoriatic patients with moderate and severe disease. Patients should be advised to inform their physicians promptly if any signs of an infection or malignancy occur while they are undergoing a course of treatment with alefacept.

The manufacturer will be selling the drug to wholesalers for about $7,000 to $10,000 for a 12-week course of treatment. Patients and insurers are likely to pay about $8,400 to $11,900, a price that is less than the cost of methotrexate ($1,000 to $2,000 per year). The drug can be taken orally.

Cyclosporine Ophthalmic Emulsion, 0.05% (Restasis™)

Manufacturer: Allergan, Inc., Irvine, CA

Indication: Treatment of keratoconjunctivitis sicca (chronic dry eye disease, or CDED) in patients whose tear production is suppressed because of eye inflammation

Drug Class: This ophthalmic emulsion contains a topical immunomodulator with anti-inflammatory activity.

Uniqueness of Drug: Cyclosporine ophthalmic emulsion increases tear production in patients with dry eyes who do not produce enough tears. Although the exact mechanism of action is not known, it is thought that the emulsion works in two ways:

- as a partial immunomodulator that produces a “T-cell effect,” which inhibits T cells from going into “battle mode” to protect the eyes from an outside attack
- as an anti-inflammatory agent that prevents T cells from releasing cytokines, proteins that initiate the inflammatory effect of chronic dry eyes

Warnings: Cyclosporine ophthalmic emulsion has not been studied in patients with a history of herpes keratitis.

Precautions: The product is for ophthalmic use only. The most common adverse effect is ocular burning (17%); other adverse events reported in 1% to 5% of patients have included conjunctival hyperemia, discharge, epiphora, eye pain, foreign body sensation, pruritus, stinging, and visual disturbances (usually blurring).

Dosage: One drop of cyclosporine ophthalmic emulsion, 0.05%, is instilled twice a day in each eye approximately 12 hours apart. The emulsion can be used along with artificial tears, allowing a 15-minute interval between administrations of both products.

P&T Committee Considerations: In patients with chronic dry eyes, the production of normal tears is decreased because of chronic eye inflammation. This condition can cause significant discomfort. Other currently available therapies include artificial tears and ointments, which provide only temporary relief of symptoms.

Cyclosporine ophthalmic emulsion, 0.05%, appears to be a superior treatment. Dry eyes are most common in women over 45 years of age, in women experiencing menopause, and in patients with immune system diseases such as arthritis. The eye’s tear film is diminished because of the inflammation. Damage to the delicate tissues in the eye can lead to impaired vision. The lack of tears can be dangerous; tears defend the eye against bacteria and flush away foreign particles.

The topical ophthalmic emulsion increases tear production to a normal volume. It is the first and only therapy for patients with keratoconjunctivitis sicca, characterized by suppressed tear production, presumably from eye inflammation.

Cyclosporine ophthalmic emulsion, 0.05%, should be placed on the formulary as primary treatment of chronic dry eye disease. Artificial tears and ointments provide only symptomatic relief and do not address inflammation; in patients who were taking a topical anti-inflammatory agent or who were using punctal plugs, no increased tear production was observed.

The average wholesale price for the single-use vials of the emulsion has not yet been determined.