Criteria for Nonformulary Use of Biologic Agents for Psoriasis

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

These criteria were based on the best clinical evidence currently available. The recommendations in this document are dynamic, and will be revised as new clinical information becomes available. This guidance is intended to assist practitioners in providing consistent, high-quality, cost-effective drug therapy. These criteria are not intended to interfere with clinical judgment; the clinician must ultimately decide the course of therapy based on individual patient situations.

Additional information on biologic agents may be found in the drug monographs for alefacept and efalizumab and the *Criteria for Use for Leflunomide, Etanercept, and Infliximab in the Treatment of Rheumatoid Arthritis*, available at www.vapbm.org or vaww.pbm.med.va.gov.

Background

Three immunosuppressive biologic agents, alefacept, efalizumab, and etanercept have been FDA-approved for the treatment of adult patients with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy (Table 1). One other biologic agent that has been shown in published clinical trials to be efficacious in moderate to severe plaque psoriasis is infliximab,[1,2] a tumor necrosis factor (TNF) antagonist. A conference proceeding also reported promising results when infliximab was evaluated in the treatment of psoriatic arthritis.[3,4] Adalimumab, also a TNF antagonist, is approved for rheumatoid arthritis and is another potential agent for plaque psoriasis; however, there are no published trials to support its use at this time. Etanercept is also approved in the U.S. for the treatment of rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis, and infliximab is approved for the treatment of rheumatoid arthritis and Crohn's disease. *The administration of infliximab or adalimumab for treatment of plaque psoriasis would currently constitute off-label use.* These criteria pertain to the four biologic agents for which there is published data on their use for psoriasis: alefacept, efalizumab, etanercept, and infliximab.

Table 1 FDA-approved Psoriasis Indications

Agent	Approval Year	Indication
Alefacept	2003	Treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy.
Efalizumab	2003	Treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.
Etanercept	1998	Reducing signs and symptoms and inhibiting the progression of structural damage of active arthritis in patients with psoriatic arthritis. Etanercept can be used in combination with methotrexate in patients who do not respond adequately to methotrexate alone.
	2004	Treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.
Adalimumab	2002	Currently not approved for psoriasis indications (and no published data for psoriasis available)
Infliximab	1998	Currently not approved for psoriasis indications.

Head-to-head trials comparing biologic agents with each other and with conventional antipsoriatic therapies are lacking. While definitive comparisons between agents cannot be made at this time, the biologic agents work by mechanisms different from those of conventional systemic agents and may offer alternatives to patients who have unsatisfactory responses to the older drugs. They also lack the major organ toxicities associated with methotrexate (cirrhosis, pulmonary fibrosis), cyclosporine (renal impairment, hypertension), and acitretin (teratogenicity, mucocutaneous toxicity). Since efalizumab and etanercept offer the possibility of self-administration of subcutaneous injections, they may be more convenient to patients than receiving office-based ultraviolet (UV) therapy.

Some factors to consider when selecting a biologic agent are shown in Table 2. Clinical trial results are summarized in Appendix 1, *Summary of Double-blind, Placebo-controlled Randomized Trials of Biologics in Plaque Psoriasis* (page 11). Treatment effects (differences in responses between biologic agents and placebo) in terms of PASI-75 responder rates between 10 and 14 weeks of therapy appear to be greater with the two anti-TNF agents, particularly infliximab. However, in the absence of head-to-head clinical trials, it is difficult to determine whether one of the biologic agents is superior. There is more postmarketing safety experience with etanercept and infliximab than the other two biologics, primarily for non-psoriasis indications (see above), although infliximab is currently not approved for plaque psoriasis.

Table 2 Comparison of Biologic Agents for Psoriasis

	Alefacept	Efalizumab	Etanercept	Infliximab
Advantages	Long remissions (> 6 mo with 1 course, > 12 mo with 2 courses)[5 6]	Self-injectable (s.c.)	Self-injectable (s.c.) Familiarity with drug; 5 years of safety experience Early onset (2 wk)[7] May be used in combination with methotrexate for psoriatic arthritis	Appears to be highly effective with early onset (2 wk)[1] May induce remissions of 6–8 mo (n = 30)[2] Familiarity with drug; 5 years of safety experience
Disadvantages	Lymphopenia; weekly CD4+ T lymphocyte counts Weekly clinic visits for injections (i.m. or i.v.) Limited long-term safety data	Seems to lose effectiveness upon retreatment of previous responders in flare Not disease-remitting; requires continuous therapy Limited long-term safety data	Development of autoantibodies; risk of rare drug-induced lupus and demyelinating disease	Inconvenient; requires clinic visits every 2 to 4 wk for infusions Clinical trials of safety and efficacy in psoriasis are still in progress Infusion reactions are common† Human Antichimeric Antibodies – associated with hypersensitivity reactions, infusion reactions, and possible loss of efficacy Development of autoantibodies; risk of rare drug-induced lupus and demyelinating disease

† Mild infusion reactions preventable with acetaminophen 325 mg, nonsedating antihistamine, or both.[2]

VA Criteria for Use

The use of biologic agents is restricted to physicians experienced in the treatment of severe psoriasis or psoriatic arthritis.

All of the following criteria must be met. **Patients must**

1. Be adults ≥ 18 years of age who have chronic (≥ 6 months) severe *plaque psoriasis* (for using any of the four biologics) or psoriatic arthritis (for etanercept). For efalizumab, patients must also have stable psoriasis for at least the previous 3 months and not be in flare. Criteria for severe psoriasis are shown on page 3.
2. Be candidates for systemic antipsoriatic therapy or ultraviolet therapy, and have documented inaccessibility to ultraviolet therapy OR documented inadequate response, contraindication, intolerance, or hypersensitivity to methotrexate AND, if available, ultraviolet therapy (PUVA or UVB) with or without oral retinoids (e.g., acitretin). The only exceptions are patients who are stable on efalizumab prescribed by a non-VA physician and who also meet VA criteria for a biologic. Until there is further information on how to safely transition to alternative therapies, these patients may remain on efalizumab to avoid the risk of psoriasis worsening or variants associated with discontinuation of the agent. If a patient has not been previously tried on methotrexate and UV therapy but meets the other VA criteria for biologic therapy, the decision to transition these patients from efalizumab to either of these therapies should be made on a case-by-case basis.
3. Have no contraindications to biologic therapy (Table 4, Contraindications) or other condition that would preclude the use of biologic agents (see Table 5, Warnings and Precautions).
4. Receive no concurrent live or live-attenuated vaccines during therapy. With efalizumab, the manufacturer recommends that patients should also not receive acellular vaccines during therapy. (Also see Table 6.)
5. Receive no concurrent immunosuppressive therapy EXCEPT those used in the treatment of psoriasis. Ultraviolet therapy with or without oral retinoids is considered by experts to be safe to use with biologic agents, although published reports of such combination therapy are lacking at this time. Methotrexate is approved for concurrent use with etanercept and infliximab. Justification for any concurrent use of systemic or other immunosuppressive antipsoriatic therapy with biologic agents (such as for transitioning or potential additive effects in partial responders) should be clearly documented. Currently, there are no published data documenting the safety of combination therapy with biologics. Current prescribing information for the biologics advise against such combinations (see Table 6, Drug Interactions and Table 7, Concomitant Medications). Therefore, clinicians should weigh the potential risks and benefits before deciding to use concurrent ultraviolet, systemic, or other immunosuppressive therapy with biologics.

Criteria for severe psoriasis[†]

(a) Disease is disabling or impairs the patient's quality of life (self-reported), including ability to work and activities of daily living AND

(b) Disease does not have a satisfactory response to treatments that have minimal risks AND

(c) The patient is willing to accept life-altering adverse effects to achieve less disease or no disease AND

(d) Generally more than 10% of body surface area is involved with disease
OR

(e) Other factors apply (patient's attitude about disease; location of disease [e.g., face, hands, fingernails, feet, genitals]; symptoms [e.g., pain, tightness, bleeding, or severe itching]; arthralgias or arthritis).

[†] Adapted from a Position Paper by Krueger, et al (2000)[8] and the National Psoriasis Foundation Medical Board Guidance for Managed Care Systems for Phototherapy or Systemic Treatments (including Biologics)[9]

Discontinuation Criteria

Minimal improvement after one course of efalizumab. Patients who have a minimal improvement after 12 wk of treatment with efalizumab 1 mg/kg s.c. weekly are unlikely to respond to further treatment.[10] These patients should be gradually withdrawn from efalizumab or carefully transitioned to alternative therapy as necessary. Avoid abrupt discontinuation of efalizumab. Response to therapy and justification for continuing efalizumab should be clearly documented.

Minimal improvement after 6 months of etanercept therapy. Patients who experience minimal improvement after 6 months of therapy with etanercept at maximal recommended maintenance doses (25 mg s.c. twice weekly for 6 months preceded by 50 mg s.c. twice weekly for the initial 12 weeks) are unlikely to gain additional benefit from continued therapy. This recommendation is based on indirect evidence showing similar response rates between a 6-month[7,11] and a 12-month[12] course at a dose of 25 mg twice weekly (Appendix 1).

When biologics are used in combination therapy with another systemic agent, the contribution each agent is providing to patient response should be considered periodically. If continued use of one agent cannot be justified against potential adverse effects and overall cost, the agent should be discontinued.

Reasons to discontinue the biologic agents related to safety concerns are listed in Table 5 (page 4).

Inappropriate Indications for Use

Routine use of any biologic agent for psoriasis types other than chronic, stable/nonflaring, moderate to severe plaque psoriasis. These agents have been demonstrated to be efficacious in the treatment of chronic, stable/nonflaring, moderate to severe plaque psoriasis. There is insufficient evidence to support their efficacy and safety in the treatment of other types of psoriasis (e.g., guttate, erythrodermic, or pustular), mild psoriasis, and psoriasis in flare, and they should not be routinely used for these conditions. Biologic agents may be considered on a case-by-case basis for non-plaque psoriasis in patients who have had inadequate responses to traditional approaches.

Use of infliximab for moderate to severe chronic heart failure, acute alcoholic hepatitis, and primary Sjogren's syndrome. There is evidence from double-blind randomized controlled trials that infliximab therapy results in lack of efficacy and harm when used for moderate to severe chronic heart failure[13] or acute alcoholic hepatitis,[14] and it is not efficacious for primary Sjogren's syndrome.[15]

Contraindications

Table 4 Contraindications

Alefacept	Efalizumab	Etanercept	Infliximab
Hypersensitivity to alefacept or any of its product components	Hypersensitivity to efalizumab or any of its components	Sepsis Hypersensitivity to etanercept or any of its product components	Hypersensitivity to any murine proteins or other product components Administration of doses > 5 mg/kg to patients with moderate to severe (NYHA class III or IV) congestive heart failure

Sources: Amevive (alefacept) package insert[16]; Raptiva (efalizumab) package insert[17]; Enbrel (etanercept) package insert[12]; Remicade (infliximab) package insert[18]

Warnings and Precautions

Table 5 Warnings and Precautions

Alefacept	Efalizumab	Etanercept	Infliximab
Do not initiate therapy if the patient has contraindications (Table 4) or...			
Has a CD4+ lymphocyte count below normal. **Has a history of systemic malignancy** Has a clinically important infection	**Has thrombocytopenia**† Has a clinically important infection	Has active infection, including chronic or localized infection	Has a clinically important, active infection
Use caution when considering agent if the patient...			
Is at high risk for malignancy Has chronic infection or history of recurrent infections **Is receiving phototherapy or other immunosuppressive agent (also see Table 6)**‡	**Is elderly (older patients have a greater risk of developing infections)** **Is at high risk for malignancy or has a history of malignancy** **Is receiving phototherapy or other immunosuppressive agent (also see Table 6)** ‡ Has chronic infection or history of recurrent infections	**Has preexisting or recent-onset CNS demyelinating disorder** **Has history of significant hematologic abnormalities** **Has heart failure** Is at high risk for malignancy or has a history of malignancy† Has a history of recurrent infections or a condition that may predispose patients to developing infections (e.g., uncontrolled diabetes)	**Has resided where histoplasmosis or coccidioidomycosis is endemic** **Has [mild] heart failure; consider other treatment options first** **Has pre-existing or recent-onset central nervous system demyelinating or seizure disorder** **Is elderly (older patients have a greater risk of developing infections)** Has chronic infection or a history of recurrent infections Is at high risk for malignancy or has a history of malignancy **Has ongoing or history of significant hematologic abnormalities**
Perform tuberculin skin test and/or chest X-ray and treat patient if positive for latent tuberculin infection...			
Before starting therapy in patients living in areas of endemic TB †	Before starting therapy in patients living in areas of endemic TB †	Before starting therapy in patients living in areas of endemic TB†	**Before starting therapy in all patients**
Monitor patient closely...			
For lymphopenia during therapy; check CD4+ T lymphocyte counts weekly If patient develops new infection	**For signs and symptoms of thrombocytopenia during therapy; check platelet count when initiating therapy (e.g., monthly) and periodically thereafter (e.g., every 3 months)** **For psoriasis worsening or variants following discontinuation of efalizumab** If patient develops new infection	**If patient has heart failure** If patient develops new infection	**For signs and symptoms of infection during and after treatment** If patient develops new infection
Discontinue therapy if the patient...			
Has CD4+ T lymphocyte counts that remain less than 250 cells/µl for one month Develops serious infection **or malignancy** Develops serious allergic reaction Develops significant clinical signs of liver injury	Develops thrombocytopenia Develops serious infection **or malignancy** Develops serious allergic reaction†	**Has significant exposure to varicella virus (discontinue temporarily); consider prophylactic treatment with Varicella Zoster Immune Globulin** Develops significant hematologic abnormality (e.g., pancytopenia, aplastic anemia) **Develops lupus-like syndrome** Develops serious infection [or malignancy†] Develops serious allergic reaction	**Develops symptoms suggestive of a lupus-like syndrome (autoimmune disorder related to autoantibodies)** **Develops new or worsening symptoms of heart failure.** Develops a serious infection [or malignancy†] Develops severe hypersensitivity reaction Develops significant hematologic abnormalities (e.g., leukopenia, neutropenia, thrombocytopenia, pancytopenia) **Develops significant central nervous system adverse reactions**

Sources: Amevive (alefacept) package insert[16]; Raptiva (efalizumab) package insert[17]; Enbrel (etanercept) package insert[12]; Remicade (infliximab) package insert[18]

Bold typeface–indicates an item that is different from at least one of the other biologic agents or an item listed in the package insert for one agent and not for at least one other agent but is recommended as part of this criteria for use guidance

† No recommendation in package insert, but recommended by this criteria for use guidance.

‡ Package insert recommends that patients should *not* receive concurrent immunosuppressives or phototherapy. These criteria advise caution.

All of the biologic agents are associated with risks of malignancy, serious infections including opportunistic infections and sepsis, and all except alefacept have been associated with possible or likely autoimmune disorders.

Chronic immunosuppression is associated with an increased risk of non-melanoma skin cancer; however, this type of cancer is not considered to be a contraindication to biologics. Caution is warranted when administering biologics to patients at high risk or with a history of malignancy given the lack of long-term safety data. Patients with a history of systemic malignancy should not receive alefacept.

Infliximab has a black box warning that emphasizes the risks of infections and tuberculosis (frequently disseminated or extrapulmonary at clinical presentation), invasive fungal infections, and other opportunistic infections, some of which have been fatal. Patients should be evaluated for latent tuberculosis infection with a tuberculin skin test and treated for any latent tuberculosis infection before beginning therapy with infliximab. The prescribing information for the other biologic agents do not recommend testing and treating for latent tuberculin infection before initiating therapy. However, since all the biologic agents are immunosuppressives that have the potential to reactive latent infections, the criteria for use of biologic agents for psoriasis recommend this practice in the VHA.

Monitoring

Alefacept

1. Alefacept causes **lymphopenia** with dose-dependent decreases in circulating CD4+ and CD8+ T lymphocyte counts. The patient's CD4+ T lymphocyte count should be monitored before starting alefacept and periodically (typically, weekly) during each 12-week course of therapy. The CD4+ T lymphocyte count should be normal before administering the initial or subsequent doses of alefacept. Withhold doses if the CD4+ T lymphocyte count is less than 250 cells/μl. Discontinue alefacept therapy if the CD4+ T lymphocyte counts remain less than 250 cells/μl for one month.
2. Physicians should monitor patients for signs and symptoms of **infection** during or after a course of alefacept. Patients who develop new infections during alefacept therapy should be closely monitored.
3. Reports of **liver injury** have been noted in postmarketing surveillance. Hepatic events include asymptomatic increases in transaminases, fatty infiltration of the liver, hepatitis, decompensation of cirrhosis with liver failure, and acute liver failure. Concomitant alcohol use was a confounding factor in two cases of liver failure. A causal relationship between hepatic injury and alefacept has not been established. Patients with signs or symptoms of hepatic injury should be fully evaluated. Discontinue alefacept in patients who develop clinical signs of hepatic injury. The prescribing information does not include recommendations for monitoring of liver enzymes. Since this is an unpredictable adverse event, monitoring of liver enzymes with CD4+ counts is not an unreasonable consideration.

Efalizumab

1. Serious, potentially autoimmune-mediated **thrombocytopenia** has been observed during efalizumab therapy. Physicians should closely monitor patients for signs and symptoms of thrombocytopenia. Check platelet counts when initiating therapy (e.g., monthly) and periodically thereafter (e.g., every 3 months). Discontinue efalizumab if a patient develops severe thrombocytopenia.
2. Patients who develop new **infections** during efalizumab therapy should be monitored.
3. Serious **worsening of psoriasis** or development of **psoriasis variants** (e.g., erythrodermic or pustular psoriasis) occurred during or after efalizumab therapy in clinical trials, particularly after patients were withdrawn from efalizumab without transitioning to alternative therapy.[19] In some cases, patients required hospitalization. Patients, including those not responding to efalizumab, should be closely monitored following discontinuation of efalizumab, and alternative antipsoriatic treatment instituted as necessary. There is no clinical evidence available to guide the selection of follow-on antipsoriatic agents upon discontinuation of efalizumab.

Etanercept

1. Serious, sometimes fatal, **infections** and sepsis have occurred during clinical trials and postmarketing. Many cases involved concomitant use of other immunosuppressive agents. Rare cases of **tuberculosis** developed in patients treated with TNF antagonists, including etanercept. The patient should be monitored closely if a new infection develops.

2. **Neurologic events**, including demyelinating disease, such as multiple sclerosis, myelitis, and optic neuritis, as well as seizures have developed or worsened in patients treated with etanercept for rheumatoid arthritis. Patients should be warned to watch for visual changes.
3. Rare cases of **blood dyscrasias**, including pancytopenia / aplastic anemia, were reported among patients treated with etanercept. Some cases were fatal. It is unclear if etanercept is causally related to these events. Physicians should advise all patients to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever, bruising, bleeding, or pallor) during etanercept therapy.
4. The results of one of two large clinical trials investigating etanercept in the treatment of **heart failure** suggested increased mortality in patients treated with etanercept compared with placebo; the results of the other trial did not corroborate these findings.[20] Worsening or new onset congestive heart failure, including cases in patients less than 50 years old or without history of cardiovascular disease, have been noted in postmarketing reports. Exercise caution and carefully monitor patients when etanercept is used in patients with preexisting heart failure.

Infliximab

1. Serious opportunistic **infections**, including coccidioidomycosis, histoplasmosis, listeriosis, pneumocystosis, **tuberculosis** (often disseminated or extrapulmonary), and other bacterial, fungal, and mycobacterial infections have been observed in patients on infliximab therapy during clinical trials as well as in postmarketing surveillance. Some cases have resulted in death. As a result of these reports, a black box warning was added to the package insert for infliximab, advising physicians to evaluate patients for latent tuberculin infection with a tuberculin skin test and to initiate treatment for latent tuberculin infection before beginning infliximab therapy. In addition, physicians should carefully weigh the risks and benefits of infliximab therapy in patients who resided in areas where coccidioidomycosis and histoplasmosis is endemic.
2. Higher rates of mortality and hospitalization due to worsening **heart failure** were observed in patients treated with infliximab, especially 10 mg/kg, during trials to evaluate its safety and efficacy in the treatment of heart failure (NYHA Class III/IV, left ventricular ejection fraction 35% or less).[18] Worsening or new onset congestive heart failure, including cases in patients less than 50 years old or without history of cardiovascular disease, have been noted in postmarketing reports. Infliximab has not been studied in patients with mild heart failure. Consider other treatment options before considering infliximab in patients with heart failure.
3. **Infusion reactions** (adverse events that occur during or within 2 hours after administration of infliximab) were common in clinical trials (20% of infliximab-treated patients versus 10% of placebo patients).[18] These reactions include fever, chills, hypotension, hypertension, chest pain, dyspnea, pruritus, urticaria, anaphylaxis, convulsions, and erythematous rash.
4. **Reactions upon readministration,** including **delayed hypersensitivity** or **serum sickness–like reactions,** have occurred in patients with Crohn's disease 3 to 12 days after infliximab was reinstituted following an extended (2- to 4-year) period off infliximab therapy. The majority of reactions (6/10, 60%) were serious.[18] Signs and symptoms included myalgia, arthralgia, fever, rash, pruritus, edema involving the face, hand, or lip, dysphagia, urticaria, sore throat, and headache. Large increases in infliximab antibodies, loss of detectable serum concentrations of infliximab, and possible loss of drug efficacy were observed. Many patients had received a liquid formulation of infliximab which is no longer in use; however, a relationship between these reactions and drug formulation is unclear. Discontinue infliximab for severe reactions. Keep medications to treat hypersensitivity reactions immediately available in case of a reaction.
5. About 10% of patients treated with infliximab develop **antibodies** which have been associated with a three-fold increased risk of infusion reactions. **Serum sickness** has been reported. Antibody formation was more frequent in patients with Crohn's disease who received infliximab for longer than 16 weeks. In patients treated with infliximab for Crohn's disease or rheumatoid arthritis, antibody formation was less common among patients concomitantly treated with immunosuppressants, including methotrexate.
6. Postmarketing surveillance has revealed cases of **hematologic abnormalities** (i.e., leukopenia, neutropenia, thrombocytopenia, and pancytopenia), some of which have been fatal. There have also been rare cases of **systemic vasculitis**. Causal relationships between either of these adverse events and infliximab have not been established.

Special Populations

Pregnancy

Agent	Category	Comments
Alefacept	B	Animal reproductive toxicology studies have found no evidence of impaired fertility or harm to the fetus due to alefacept. The risks on pregnancy and fetal development, including immune system development, are not known. Health care providers are encouraged to enroll patients who become pregnant during alefacept therapy or within 8 weeks of discontinuing alefacept into the Biogen Pregnancy Registry (call 1-866-AMEVIVE or 1-866-263-8483).
Efalizumab	C	It is unknown whether there is risk of fetal harm, maldevelopment of the fetal immune system, and effects on reproductive capacity when efalizumab is administered to pregnant women. Administer to pregnant women only if clearly needed. Health care providers are encouraged to enroll patients who become pregnant during efalizumab treatment or within 6 weeks of discontinuing efalizumab into the RAPTIVA Pregnancy Registry (call Genentech Product Safety at 1-888-835-2555).
Etanercept	B	Animal developmental toxicity studies have found no evidence of fetal harm due to etanercept. Studies have not been performed in pregnant women. Use etanercept during pregnancy only if clearly needed.
Infliximab	B	Animal developmental toxicity studies have found no evidence of maternal toxicity, embryotoxicity, or teratogenicity. Animal reproduction studies found no adverse effects after administration of doses up to 40 mg/kg. Risks to a human fetus and effects on reproductive capacity are unknown. Give to pregnant women only if clearly needed.

Sources: Amevive (alefacept) package insert[16]; Raptiva (efalizumab) package insert[17]; Enbrel (etanercept) package insert[12]; Remicade (infliximab) package insert[18]

Nursing Mothers

It is not known whether the four biologic agents are excreted in human milk. With efalizumab, animal data suggest the potential for nursing infants to have reduced ability to mount an antibody response.[17] Consider options to either discontinue nursing or discontinue use of biologic agents.

Elderly

The use of biologic agents in elderly patients (65 years or older) is limited. No apparent differences in safety or efficacy have been observed between older and younger patients for any of the agents; however, the number of elderly patients may have been insufficient to detect true differences. Prescribing information for efalizumab and infliximab contain cautions when using biologic agents in elderly patients because of their increased risk for infections.

Drug Interactions

Drug interaction studies have not been performed with alefacept, efalizumab, etanercept, and infliximab.

Table 6 Drug Interactions

	Possible effect and Recommendation			
Concomitant Agent	**Alefacept**	**Efalizumab**	**Etanercept**	**Infliximab**
Anakinra	—	—	Increased infection rate. No specific recommendations.	—
Phototherapy and other immunosuppressants	Weigh potential risks and benefits before concurrent use.[†‡]	Weigh potential risks and benefits before concurrent use.[†]	Methotrexate and glucocorticoids may be given concomitantly. Weigh potential risks and benefits before concurrent use.[§]	May administer concurrently with methotrexate; however, increased infliximab serum concentrations have been observed (clinical relevance is uncertain). Co-administration with immunosuppressants appears to reduce the frequencies of antibodies to infliximab and infusion reactions. Weigh potential risks and benefits before concurrent use.[§]

Concomitant Agent	Possible effect and Recommendation			
	Alefacept	**Efalizumab**	**Etanercept**	**Infliximab**
Acellular vaccines	Immune response preserved with tetanus toxoid and an experimental neo-antigen. No specific recommendations.	Decreased immune response to tetanus toxoid in animals and to neoantigen in humans. Prescribing information recommends avoiding concurrent use. If possible, vaccinate before starting efalizumab. Weigh potential risks and benefits before deciding to vaccinate during therapy.	Not studied; effective immune response with pneumococcal polysaccharide vaccine; non-live vaccines may be given concurrently.	Not studied. Possible decreased immune response. No specific recommendations.
Live and live-attenuated vaccines	Not studied; possible disseminated infection. Avoid concurrent use.	Not studied; possible disseminated infection and lack of immune response. Avoid concurrent use.	Possible disseminated infection; effective B-cell immune responses to pneumococcal polysaccharide but lower antibody titers. Avoid concurrent use.	Not studied; possible disseminated infection and lack of immune response. Avoid concurrent use.

Sources: Amevive (alefacept) package insert[16]; Raptiva (efalizumab) package insert[17]; Enbrel (etanercept) package insert[12]; Remicade (infliximab) package insert[18]

† Prescribing information warns of possible excessive immunosuppression and advises to avoid concurrent use of phototherapy or other immunosuppressive agent with alefacept and efalizumab. No warning to avoid phototherapy or other immunosuppressive agent is given for etanercept and infliximab.

‡ The duration of time to wait between discontinuing alefacept and starting other immunosuppressive therapy has not been evaluated.

§ Prescribing information gives no specific recommendations for phototherapy.

Expert opinion considers concomitant use of phototherapy with biologic agents to be relatively safe. Unpublished subanalyses from two phase III trials involving alefacept for psoriasis suggest that concomitant use with nonspecific immunosuppressants may not pose additional risks; ongoing trials will directly address this issue.[21] An ongoing trial with continuous efalizumab therapy for 3 years allows the use of UVB therapy following an initial 3-month treatment period; however, there has been no subgroup analysis (written communication, Genentech Medical Communications, 17 June 2004). Cyclosporine has been used concurrently with efalizumab during a 5-week transition period in one case report.[22] Although there has been a report that efalizumab (0.5 to 2 mg/kg/wk for 12 weeks) was used safely with dual immunosuppressant therapy (cyclosporine and either mycophenolate mofetil or sirolimus) for renal transplant,[23] in other early clinical trials, potentially fatal post-transplant lymphoproliferative disorder was observed when efalizumab (2 mg/kg/wk for 12 weeks) was used in combination with triple immunosuppressive therapy (cyclosporine, mycophenolate mofetil, and prednisone).[19,24] There is no published information regarding the concurrent use of methotrexate or systemic corticosteroids with efalizumab (written communication, Genentech Medical Communications, 17 June 2004).

Table 7 Concomitant Medications

	Alefacept	Efalizumab	Etanercept	Infliximab
Permitted in psoriasis clinical trial protocols	Limited application of moderate-potency glucocorticoids, keratolytics, coal tar, or calcipotriene to groin, scalp, palms, and soles Emollients	Eucerin cream, tar or salicylic acid preparation for psoriasis on the scalp Limited application of low-potency glucocorticoids Oral antipruritic agents	Methotrexate ≤ 25 mg/wk Glucocorticoids Salicylates Nonsteroidal anti-inflammatory drugs Analgesics Vaccinations except live vaccines	Nonmedicinal emollients Nonprescription tar or salicylic shampoos
Not Permitted in psoriasis clinical trial protocols	Systemic treatments, phototherapy, high-potency topical glucocorticoids	Other systemic or UV therapy for psoriasis Other immuno-suppressive therapy Acellular, live, and live-attenuated vaccines	Live vaccines	Systemic therapy (UVB, PUVA, cyclosporine, methotrexate[†], or acitretin) Topical therapy

Sources: Amevive (alefacept) package insert[16]; Raptiva (efalizumab) package insert[17]; Enbrel (etanercept) package insert[12]; Remicade (infliximab) package insert[18]; Ortonne (2003)[25]; Lebwohl (2003)[26]

[†] Methotrexate was allowed in rheumatoid arthritis and Crohn's disease trials

Dosage and Administration

Table 8 Dosage Regimens for Adults

	Alefacept	Efalizumab	Etanercept	Infliximab
Indication	Moderate to severe plaque psoriasis	Moderate to severe plaque psoriasis	Psoriatic arthritis Moderate to severe plaque psoriasis	Moderate to severe plaque psoriasis (off-label use) Active psoriatic arthritis (insufficient data to support this off-label use)[†]
Initial dose	15 mg i.m.	0.7 mg/kg s.c. x 1 (conditioning dose)	*Psoriatic arthritis*: 25 mg s.c. or 50 mg s.c. *Plaque psoriasis*: 50 mg s.c. (25 mg is also efficacious)	5 or 10 mg/kg i.v. infusion over 2 h (studied in plaque psoriasis) 5 mg/kg over 2 h (studied in psoriatic arthritis) CHF: Max. 5 mg/kg i.v.
Subsequent and maintenance doses	15 mg i.m. weekly	1 mg/kg s.c. weekly	*Psoriatic arthritis*: 25 mg s.c. twice weekly 72 to 96 h apart or 2 x 25-mg s.c. doses on the same day once weekly *Plaque psoriasis*: 50 mg s.c. twice weekly (3 to 4 days apart) for 3 mo then step down to 50 mg/wk (25 or 50 mg/wk is also efficacious). Consider "step-up" therapy, starting with 25 mg/wk.)	5 or 10 mg/kg i.v. at wk 0, 2, and 6 (induction); nonresponders were re-dosed at wk 10, 12, and 16 (studied in plaque psoriasis); optimal maintenance regimen has not been determined. 5 mg/kg i.v. at wk 0, 2, 6, and 14 then every 8 wk (studied in psoriatic arthritis)
Duration	12 wk; may repeat 12-wk course once, at least 12 wk after the previous course	Continuous	Continuous (studied up to 12 mo in plaque psoriasis)	Studied up to 16 wk in plaque psoriasis Studied up to 54 wk in psoriatic arthritis
Maximum recommended dose	15 mg / wk i.m.	200 mg / dose	*Psoriatic arthritis*: 50 mg once weekly *Plaque psoriasis*: 50 mg twice weekly	Studied up to 10 mg/kg
After Discontinuation	—	Monitor patient closely for worsening of psoriasis and institute alternative antipsoriatic treatment as necessary.	—	—

Sources: Amevive (alefacept) package insert[16]; Raptiva (efalizumab) package insert[17]; Enbrel (etanercept) package insert[12]; Remicade (infliximab) package insert[18]; clinical trial publications[1,2,7,11]. [†] Published abstract only[3,4]

Efalizumab should not be abruptly discontinued without close monitoring or drug transitioning, even in patients who are worsening or not responding on treatment.[19] Appropriate follow-on therapies have not been evaluated in clinical trials. The safety of using efalizumab concomitantly with antipsoriatic medications other than some topical medications has not been evaluated.

Efalizumab and etanercept are intended for use under the guidance and supervision of a physician. If determined to be appropriate, self-injection of the drug is possible after the patient receives proper training in reconstitution and administration techniques.

Alefacept injections and infliximab infusions should be given by trained health care personnel.

Drug and Biologic Agent Acquisition Costs

Table 9 Costs of Systemic Antipsoriatic Agents

Drug	Dosage Regimen	Route	Duration (wk)	Cost of Treatment Course Per Patient	Estimated Courses Per Year	Estimated Yearly Cost Per Patient
Agents on VA National Formulary						
Methotrexate	7.5–25 mg/wk	i.m./i.v.	12	$1.50–$5.02	Continuous	$6.50–$21.33
	7.5–25 mg/wk	p.o.	12	$9.00–$30.00	Continuous	$37.50–$130.00
Methoxsalen†	40 mg/d 2–3 d/wk (for 70 kg)	p.o.	4–8	$120.08–$360.23	2–3	$240.16–$1,080.69
Cyclosporine	175–350 mg/d (2.5–5 mg/kg/d x 70 kg)	p.o.	16	$431.76–$863.29	1	$431.76–$863.29
Acitretin†	25–50 mg/d	p.o.	12	$562.27–$1,124.54	2–3	$1,124.54–$3,373.62
Biologic Agents (Nonformulary)						
Alefacept	15 mg/wk	i.m.	12	$6968	2	$13,936
Efalizumab	70 mg/wk (1 mg/kg/wk)	s.c.	12	$2458	Continuous	$10,651
Etanercept	50 mg twice weekly	s.c.	12	$4320	1	$4320
	50 mg/wk	s.c.	12	$2160	3 + Initial 12 wk (Continuous)	$11,448 ($9360)
	25 mg/wk	s.c.	12	$1080	3 + Initial 12 wk (Continuous)	$7884 ($4644)
Infliximab	350–700 mg 3x/6 wk, then about once every 8 wk as needed‡	i.v.	6	$4671–$8175	6	$28,026–$49,050

Lowest VA drug costs as of January 2004; even lower costs possible for cyclosporine with Blanket Purchase Agreement

† Administered with PUVA; cost does not include PUVA

‡ Psoriasis regimen not established. A more recent unpublished phase II trial used a lower dose (3 to 5 mg/kg 3 times / 6 weeks then about once every 8 weeks as needed).[27]

Appendix 1. Summary of Double-blind, Placebo-controlled Randomized Trials of Biologics in Plaque Psoriasis

Reference Country Trial Design (Jadad Score, 0–5)	Major Eligibility Criteria	Baseline PASI score (0–72), mean (median)	Baseline PGA Moderate to Severe, % patients	PASI-75, ARR, % patients [95% CI]	PASI-50, ARR, % patients [95% CI]	PGA Clear / Almost Clear, ARR, % patients [95% CI]	QoL Improved	Time Point, wk
Alefacept 0.075 mg/kg i.v. weekly for 12 wk								
Ellis (2001)[28] U.S. MC DB PC PG RCT (4)	Age 18 to 70 yr; chronic plaque psoriasis diagnosed at least 12 mo before and involving ≥ 10% BSA; previously received systemic treatment or phototherapy or candidates for such treatment	(15)	91%	23%	33%	19%	—	14
Alefacept 7.5 mg i.v. weekly for 12 wk								
Krueger (2002)[6] U.S. MC DB PG PC RCT (3)	Adults at least 16 yo with chronic plaque psoriasis for at least 12 mo and involving ≥ 10% of BSA; CD4+ count above lower limit of normal	—	93% to 94%	10% [6–15]	28%	7% [3–12]	—	14
Alefacept 15 mg i.m. weekly for 12 wk								
Ortonne (2003)[25] (3) and Finlay (2003)[29] (3) U.S., Europe, Canada Phase III MC DB PC PG RCT	At least 18 yo; chronic plaque psoriasis for more than 1 yr; at least 10% BSA involvement; normal CD4+ count; normal hepatic, renal, and hematologic laboratory values	(13)	83%	16%	—	16%	Yes	14
Lebwohl (2003)[26] (4) and Finlay (2003)[29] (3) U.S., Europe, Canada Phase III MC DB PC PG RCT, extension of Ortonne (2003)[25]	Adults at least 18 yo; chronic plaque psoriasis for more than 1 yr; 10% or more BSA involvement; normal CD4+ count	(13)	85%	20%	22%	16%	Yes	24
Efalizumab 0.7 mg/kg x 1 then 1 mg/kg/wk s.c. x 11 wk (total 12 wk)								
Gordon (2003)[30] U.S., Canada Phase III MC DB PC PG RCT (3)	Age 18 to 75 years; plaque psoriasis for at least 6 months; PASI ≥ 12.0 at screening, at least 10% total body surface area affected, candidate for systemic therapy	19	—	22% [15.8–29.5]	45%	23%	Yes	12
Lebwohl (2003)[10] U.S., Canada Phase III MC DB PC PG RCT (5)	Age 18 to 70 years; plaque psoriasis that had been clinically stable for at least 3 months and moderate to severe for at least 6 months, PASI of at least 12.0 at screening, plaque psoriasis covering at least 10% of the body-surface area, candidacy for systemic therapy	20	—	17%	36%	—	—	12
Etanercept 50 mg s.c. twice weekly x 12 wk then 25 mg s.c. twice weekly x 36 wk								
Unpublished "Study II" (Package Insert[12] MC DB PC PG RCT	Adults with chronic stable plaque psoriasis involving ≥ 10% of BSA; minimum PASI of 10; received or were candidates for systemic therapy or phototherapy	—	—	43% [36–51]†	64% [56–71]	50% [43–58]	—	12
Etanercept 25 mg s.c. twice weekly x 48 wk								
Unpublished "Study II" (Package Insert[12] MC DB PC PG RCT	Adults with chronic stable plaque psoriasis involving ≥ 10% of BSA; minimum PASI of 10; received or were candidates for systemic therapy or phototherapy	—	—	29% [23–36]	52% [44–60]	34% [26–41]	—	12
Etanercept 25 mg s.c. twice weekly x 24 wk								
Leonardi (2003)[11] U.S. Phase III MC DB PC PG RCT (4)	At least 18 yo; active but clinically stable plaque psoriasis involving at least 10% of BSA; minimum PASI of 10 (indicating moderate-to-severe psoriasis); previous phototherapy or systemic psoriasis therapy at least once or had been a candidate for such therapy	19	— (23% had marked or severe psoriasis)	30%	44%	29%	Yes	12
Gottlieb (2003)[7] U.S. MC DB PC PG RCT (5)	At least 18 yo; active, stable plaque psoriasis involving ≥ 10% of BSA; at least 1 previous systemic psoriasis therapy or phototherapy	18	—	28% 51%	59% 64%	— —	— Yes	12 24
Etanercept 25 mg s.c. once weekly x 24 wk								
Leonardi (2003)[11] U.S. Phase III MC DB PC PG RCT (4)	At least 18 yo; active but clinically stable plaque psoriasis involving at least 10% of BSA; minimum PASI of 10 (indicating moderate-to-severe psoriasis); previous phototherapy or systemic psoriasis therapy at least once or had been a candidate for such therapy	18	— (21% had marked or severe psoriasis)	10%	27%	18%	Yes	12
Infliximab 5–10 mg/kg i.v. over 2 h at wk 0, 2, and 6								
Chaudhari (2001) U.S. SC DB PC PG RCT (4)	Moderate to severe plaque psoriasis for at least 6 mo, involving at least 5% of BSA; topical corticosteroid failure; no previous immunobiologicals; clear chest X-ray within 1 mo; good general health	22–27	—	64% [20–90] (5 mg/kg) 55% [9–85] (10 mg/kg)	—	— (64%–73% for rPGA Good / Excellent / Clear)	—	10 wk

ARR: Absolute Risk Reduction, the difference in response between biologic agent and placebo. **PASI**: Psoriasis Area and Severity Index; 0 = no disease, 72 = maximal disease. **PASI-75** and **PASI-50**: 75% or 50% reduction in the Psoriasis Area and Severity Index; note that the time points for these PASI assessments varied across studies. **PGA**: Physician's Global Assessment or static PGA (**sPGA**); 7-point scale ranging from 0 (clear) to 6 (severe) ; another static global assessment instrument is the Overall Lesion Severity Scale (**OLS**), a 6-category scale ranging from clear to very severe. **rPGA**: Relative Physician's Global Assessment; PGA relative to baseline. **QoL**: Quality of Life; all the studies used the Dermatology Life Quality Index (DLQI); Finlay, et al (2003) also used the Dermatology Quality of Life Scales (DQOLS) and the Short Form-36 Health Survey (SF-36).

† Of 91 PASI-75 responders on etanercept 50 mg twice weekly at 12 weeks, 70 (77%) who had stepped down to 25 mg twice weekly after the initial 12 weeks maintained their PASI-75 response at 24 weeks.

References

1. Chaudhari U, Romano P, Mulcahy LD, Dooley LT, Baker DG, Gottlieb AB. Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: a randomised trial. *Lancet* 2001;357:1842-7.
2. Gottlieb AB, Chaudhari U, Mulcahy LD, Li S, Dooley LT, Baker DG. Infliximab monotherapy provides rapid and sustained benefit for plaque-type psoriasis. *J Am Acad Dermatol* 2003;48:829-35.
3. Antoni C, Kavanaugh A, B. K, et al. The infliximab multinational psoriatic arthritis controlled trial (IMPACT). Presentation at:. Presented at the American Academy of Dermatology 61st Annual Meeting; March 21-26, 2002; San Francisco, CA.
4. Antoni C, Kavanaugh A, Kirkham B, et al. The infliximab multinational psoriatic arthritis controlled trial (IMPACT) [abstract]. Presented at the American College of Rheumatology 66th Annual Meeting; October 25-29, 2002; New Orleans, LA.
5. Krueger GG, Ellis CN. Alefacept therapy produces remission for patients with chronic plaque psoriasis. *Br J Dermatol* 2003;148:784-8.
6. Krueger GG, Papp KA, Stough DB, Loven KH, Gulliver WP, Ellis CN. A randomized, double-blind, placebo-controlled phase III study evaluating efficacy and tolerability of 2 courses of alefacept in patients with chronic plaque psoriasis. *J Am Acad Dermatol* 2002;47:821-33.
7. Gottlieb AB, Matheson RT, Lowe N et al. A randomized trial of etanercept as monotherapy for psoriasis. *Arch Dermatol* 2003;139:1627-32; discussion 1632.
8. Krueger GG, Feldman SR, Camisa C et al. Two considerations for patients with psoriasis and their clinicians: what defines mild, moderate, and severe psoriasis? What constitutes a clinically significant improvement when treating psoriasis? *J Am Acad Dermatol* 2000;43:281-5.
9. NPF. When are patients candidates for phototherapy or systemic treatments (including biologics)? National Psoriasis Foundation Medical Board Guidance for Managed Care Systems. Available at: http://www.psoriasis.org/medical/advocacy/2003_systemicsdiagram.php. Accessed 16 June 2004.
10. Lebwohl M, Tyring SK, Hamilton TK et al. A novel targeted T-cell modulator, efalizumab, for plaque psoriasis. *N Engl J Med* 2003;349:2004-13.
11. Leonardi CL, Powers JL, Matheson RT et al. Etanercept as monotherapy in patients with psoriasis. *N Engl J Med* 2003;349:2014-22.
12. Wyeth Laboratories. Enbrel (Etanercept) [package insert online]. 30 April 2004. Available at: http://www.wyeth.com/content/ShowLabeling.asp?id=101. Accessed 10 May 2004. Amgen and Wyeth Pharmaceuticals.
13. Chung ES, Packer M, Lo KH, Fasanmade AA, Willerson JT. Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor-alpha, in patients with moderate-to-severe heart failure: results of the anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial. *Circulation* 2003;107:3133-40.
14. Naveau S, Chollet-Martin S, Dharancy S et al. A double-blind randomized controlled trial of infliximab associated with prednisolone in acute alcoholic hepatitis. *Hepatology* 2004;39:1390-7.
15. Mariette X, Ravaud P, Steinfeld S et al. Inefficacy of infliximab in primary Sjogren's syndrome: results of the randomized, controlled Trial of Remicade in Primary Sjogren's Syndrome (TRIPSS). *Arthritis Rheum* 2004;50:1270-6.
16. Biogen Inc. Amevive (Alefacept) package insert online. Available at: http://www.amevive.com/amevive_web/web_content/en_US/forms/AMEVIVE_Label_I63007_1.pdf. In. Cambridge, MA: Biogen Inc.; 2004.
17. Genentech. RAPTIVA (efalizumab) package insert online. Available at: http://www.gene.com/gene/common/inc/pi/raptiva.jsp. In. San Francisco, CA: Genentech, Inc.; 2003.
18. Centocor. Remicade (Infliximab) package insert. In. Malvern, PA: Centocor, Inc.; 2004.
19. BLA-STN 125075/0, Efalizumab (Raptiva). Food and Drug Administration Center for Drug Evaluation and Research, Meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee (September 9, 2003) [transcript]. 9 September 2003. Available at: http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3983T1.DOC. Accessed 18 November 2003.
20. Wyeth Laboratories. Enbrel (Etanercept) [package insert online]. 17 October. Available at: http://www.wyeth.com/content/ShowLabeling.asp?id=101. Accessed 26 February 2004. Wyeth Pharmaceuticals.
21. Vaishnaw A, Lee S. Concomitant use of alefacept and immunosuppressants in patients with psoriasis [poster exhibit P620]. Presented at the American Academy of Dermatology, 61st Annual Meeting, March 21-26, 2003; March 21-26, 2003 2003; San Francisco.
22. Hamilton TK. Initiating efalizumab therapy in patients currently treated with other systemic therapies (poster). Presented at the 10 th International Psoriasis Symposium; 10-13 June 2004; Toronto, Ontario, Canada.
23. Dedrick RL, Walicke P, Garovoy M. Anti-adhesion antibodies efalizumab, a humanized anti-CD11a monoclonal antibody. *Transpl Immunol* 2002;9:181-186.
24. Papadopoulos E. Biologic License Application STN BL 125075/0: Efalizumab for the Treatment of Chronic Plaque Psoriasis [Food and Drug Administration clinical reviewer's slide presentation to Dermatologic and Ophthalmic Drugs Advisory Committee, September 9, 2003]. Available at: http://www.fda.gov/ohrms/dockets/ac/03/slides/3983S1_03_FDA-Efalizumab.ppt. Accessed 10 December 2003.
25. Ortonne JP. Clinical response to alefacept: results of a phase 3 study of intramuscular administration of alefacept in patients with chronic plaque psoriasis. *J Eur Acad Dermatol Venereol* 2003;17 Suppl 2:12-6.
26. Lebwohl M, Christophers E, Langley R, Ortonne JP, Roberts J, Griffiths CE. An international, randomized, double-blind, placebo-controlled phase 3 trial of intramuscular alefacept in patients with chronic plaque psoriasis. *Arch Dermatol* 2003;139:719-27.

27. Campbell M. Infliximab effectively treats psoriasis. Dermatology Times (online). April 1, 2004. 1 April. Available at: http://www.dermatologytimes.com/dermatologytimes/article/articleDetail.jsp?id=93759.
28. Ellis CN, Krueger GG. Treatment of chronic plaque psoriasis by selective targeting of memory effector T lymphocytes. *N Engl J Med* 2001;345:248-55.
29. Finlay AY, Salek MS, Haney J. Intramuscular alefacept improves health-related quality of life in patients with chronic plaque psoriasis. *Dermatology* 2003;206:307-15.
30. Gordon KB, Papp KA, Hamilton TK et al. Efalizumab for patients with moderate to severe plaque psoriasis: a randomized controlled trial. *JAMA* 2003;290:3073-80.

Prepared August 2004. Contact: F. Goodman, PharmD, BCPS