National PBM Drug Monograph
Alefacept (Amevive®)
VHA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel

Introduction[1,2]

Psoriasis is a chronic, inflammatory, hperproliferative disease of varying severity, which affects the skin and joints. The prevalence varies between approximately 0.5% to 4.5% depending on country and race. It tends to be more frequent at higher latitudes and more common in Caucasians than in other races. The National Psoriasis Foundation estimates that between $1.6 and $3.2 billion is spent each year in the U.S. on psoriasis treatments alone.

The most common form of psoriasis is plaque psoriasis, which accounts for more than 80% of the cases. Plaques psoriasis is characterized by sharply demarcated, erythematous, scaling plaques that typically affect the elbows, knees, scalp and intergluteal cleft. It is widely accepted that the pathogenesis of psoriasis is an autoimmune process in which T-cell activation plays a prominent role. T-cell activation requires at least two signals – one when an antigen associated with the major histocompatibility complex (MHC) of antigen presenting cells interacts with a T-cell receptor, and another co-stimulatory signal must be delivered to the T-cell from the antigen presenting cell. One such co-stimulatory signal involves the interaction of leukocyte function antigen-3 (LFA-3) and CD2 on the T-cell. Once this interaction occurs, T-cells proliferate, with some becoming memory cells ($CD4^+CD45RO^+$ & $CD8^+CD45RO^+$). These memory cells play a critical role in the pathogenesis of psoriasis. Extravasation of these cells through the endothelium at sites of inflammation in the skin occurs and secretion of cytokines (e.g. interferon γ, interleukin 2, tumor necrosis factor α) into the dermis or epidermis leads to proliferation of immature keratinocytes and associated vascular changes. Treatment of psoriasis may include topical therapies (e.g. corticosteroids, tars, vitamin D analogs), phototherapy (PUVA, UVB), systemic therapies (e.g. methotrexate, cyclosporine, retinoids) or combinations of these.

Alefacept is a fully human, recombinant, immunosuppressive dimeric fusion protein developed by the University of Michigan and Biogen Inc. and approved by the FDA in January of 2003 for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy.

Pharmacology[2,3]

Alefacept consists of the first extracellular domain of LFA-3 fused to the Fc portion of human IgG1. The interaction between LFA-3 on antigen-presenting cells and CD2, a T-cell and natural killer (NK) cell costimulatory receptor, is blocked by the LFA-3 terminus of alefacept, resulting in inhibition of T-cell activation and proliferation. This interaction preferentially occurs on cells expressing the highest levels of CD2, i.e. the memory effector (CD45RO+) T-cell subset, which are the predominant type of infiltrating lymphocytes in psoriatic lesions. In addition to inhibiting T-cell activation and proliferation, T-cell apoptosis results from the simultaneous binding of the IgG1 portion of alefacept to FcγRIII on the surface of NK cells.

CD2 is also expressed at low levels on the surface of naïve CD4+ and CD8+ T-lymphocytes. In clinical trials, alefacept produced a dose-dependent reduction in total, CD4+, and CD8+ lymphocyte counts. Serious infections were reported in a small percentage of alefacept-treated patients (0.7-1.5%).

Pharmacokinetics[2,4]

The pharmacokinetic profile of alefacept has not been fully elucidated. In one small study the pharmacokinetics, biologic activity and tolerability of alefacept was evaluated in normal volunteers. Subjects received single doses of alefacept by intravenous (IV) bolus injection or by intramuscular (IM) injection. The following table summarizes the results of the pharmacokinetics portion of this trial.

Parameter	Alefacept 0.15 mg/kg Intravenous Bolus[a]	Alefacept 0.04 mg/kg Intramuscular inj[a]
C_{max} (μg/mL)	3.1 ± 0.4	0.36 ± 0.19
T_{max} (hr)	0.4 ± 0.2	86 ± 60
AUC $_{0\text{-last}}$ (μ · hr/mL)	516 ± 107	94 ± 58
AUC $_{0\text{-}\infty}$ (μ · hr/mL)	651 ± 142	140 ± 82
V_z (mL/kg)	90 ± 20	130 ± 44[b]
Cl (mL/hr/kg)	0.24 ± 0.05	0.34 ± 0.13[b]
$T_{1/2\ elimination}$ (hr)	266 ± 65	289 ± 123

[a] Mean ± SD
[b] Unadjusted for bioavailability

Onset & Duration: Results from phase II and phase III clinical trials demonstrated improvement in Psoriasis Area Activity Index (PASI) scores within one month following weekly IV administration of alefacept and within 3 months following weekly IM administration. Following the completion of a 12-week course of therapy (IV or IM), the duration of response is reported to be approximately 6-18 months. A mean elimination half-life of 37 days is reported in patients with chronic plaque psoriasis receiving weekly injections of alefacept. This is in contrast to an elimination half-life of approximately 11-12 days following single IV or IM injections in normal volunteers. There is a paucity of data regarding the metabolic fate and excretion of alefacept.

FDA Approved Indications[2]

Alefacept (Amevive®) is indicated for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy.

Current VA National Formulary Status

Alefacept is not currently on the VA National Formulary.

Dosage and Administration[2]

Alefacept is approved for both IV bolus and IM administration.

The recommended dose of alefacept is 7.5 mg given once weekly as an IV bolus over no more than 5 seconds, or 15 mg given once weekly as an IM injection. The recommended regimen is a course of 12 weekly injections. Re-treatment with an additional 12-week course may be considered provided that CD4+ T-lymphocyte counts are within normal limits, and a minimum of a 12-week interval has passed since the previous course of treatment. Data on more than two, 12-week treatment cycles are limited.

The CD4+ T-lymphocyte counts of patients receiving alefacept should be monitored weekly before initiating dosing and throughout the course of the 12-week dosing regimen. Dosing should be withheld if CD4+ counts are below 250 cells/μL and discontinued if the counts remain below 250 cells/μL for one month.

Adverse Effects[2,3,5,6,7,8,9]

The most serious adverse reactions reported during phase II and III clinical trails included lymphopenia, malignancies, serious infections and hypersensitivity reactions (see Precautions, Warnings).

In the 24-week period constituting the first course of placebo-controlled studies, the incidence of malignancies was 1.3% (11/876) compared to 0.5% (2/413) in the placebo group. The incidence of serious infections (requiring hospitalization) was 0.9% (8/876) in the alefacept-treated patients and 0.2% (1/413) in the placebo group. Angioedema and urticaria was reported in 2 and 6 patients receiving alefacept, respectively.

Lymphopenia (CD4+ lymphocyte levels <250 cells/μL) was the adverse event most commonly resulting in discontinuation of treatment with alefacept. In a study in which patients were randomized to receive one or two 12-week courses of IV alefacept therapy, 10% of patients temporarily discontinued treatment due to CD4+ T-

lymphocyte levels <250 cells/μL. During the first course of therapy, 22% of patients had total lymphocyte counts below normal, 48% had CD4+ T-lymphocyte counts below normal and 59% had CD8+ T-lymphocyte counts below normal. During a second course of alefacept therapy 17%, 44% and 56% of patients had total lymphocyte, CD4+ and CD8+ T-lymphocyte counts below normal, respectively. In a study of IM administered alefacept, 4% of patients temporarily discontinued treatment due to CD4+ lymphocyte levels <250 cells/μL. In this study 10%, 28% and 42% of patients had total lymphocyte, CD4+ and CD8+ T-lymphocyte counts below normal, respectively.

T-Lymphocyte Cell Line	Affect of Alefacept on Circulating T-Lymphocytes (% of patients)		
	Alefacept IV – 1st Course	Alefacept IV – 2nd Course	Alefacept IM
CD4+ <250 cells/μL	10%	--	4%
Total lymphocyte count < normal	22%	17%	10%
CD4+ < normal	48%	44%	28%
CD8+ < normal	59%	56%	42%

The following tables summarize the adverse events reported in two phase III, placebo-controlled trials. In the first trial, patients were randomized to receive one or two 12-week courses of alefacept 7.5 mg administered by IV bolus. In the second trial, patients were randomized to receive placebo, alefacept 10 mg, or alefacept 15 mg administered by IM injection.

Adverse Event	Course 1* No. (%)		Course 2# (no. (%)
	Placebo (n=186)	Alefacept 7.5 mg IV (n=367)	Alefacept 7.5 mg IV (n=153)
Accidental injury	30 (16)	73 (20)	28 (18)
Headache	38 (20)	62 (17)	18 (12)
Pharyngitis	23 (12)	52 (14)	20 (13)
Rhinitis	21 (11)	43 (12)	13 (8)
Pruritus	16 (9)	40 (11)	5 (3)
Chills	2 (1)	37 (10)	6 (4)
Flu syndrome	15 (8)	37 (10)	18 (12)
Infection	20 (11)	35 (10)	16 (10)

Adverse Event	Placebo (n=168)	Alefacept 10 mg (n=173)	Alefacept 15 mg (n=166)	Total Alefacept (n=339)
Headache	26 (15%)	34 (20%)	30 (18%)	64 (19%)
Pruritus	16 (10)	24 (14)	30 (18)	54 (16)
Infection	19 (11)	25 (14)	26 (16)	51 (15)
CD4+ count < 250/μL	0	1 (<1)	1 (<1)	2 (<1)
Pharyngitis	15 (9)	20 (12)	20 (12)	40 (12)
Accidental injury	19 (11)	22 (13)	16 (10)	38 (11)
Rhinitis	11 (7)	24 (14)	9 (5)	33 (10)
Asthenia	18 (11)	10 (6)	18 (11)	28 (8)

Approximately 3% of patients receiving alefacept developed low-titer antibodies to the drug, but no apparent correlation of antibody development and clinical response or adverse event was noted.

Rare cases of alefacept-associated transaminase elevations up to 5-10 times the upper limit of normal have been reported.

Precautions and Contraindications[2]

Alefacept is contraindicated in patients with a prior hypersensitivity to alefacept.

Effects on Immune System: Patients receiving other immunosuppressive therapy or phototherapy should not receive concurrent therapy with alefacept due to the possibility of excessive immunosuppression.

The safety and efficacy of vaccines administered to patients being treated with alefacept have not been studied. In a study of patients with chronic plaque psoriasis, the ability to mount immunity to tetanus toxoid and an experimental neo-antigen was preserved in those undergoing alefacept therapy.

Allergic Reactions: Hypersensitivity reactions (urticaria, angioedema) have been reported with the administration of alefacept.

Carcinogenesis, Mutagenesis, Fertility: In a primate chronic toxicity study, one animal in a high-dose group (20 mg/kg) developed a B-cell lymphoma that was detected after 28-weeks of dosing. Additional animals developed B-cell hyperplasia of the spleen and lymph nodes. In a separate study, centroblast proliferation in B-cell dependent areas in the germinal centers of the spleen were reported in baboons given 3 doses of alefacept at 1 mg/kg every 8-weeks.

Pregnancy/Nursing (category B): The effect of alefacept on pregnancy and fetal development is not known. Health care providers are encouraged to enroll patients who become pregnant while using alefacept into the Biogen Pregnancy Registry by calling 1-866-AMEVIVE (1-866-263-8483). It is not known whether alefacept is excreted in human milk.

Warnings[2]

Lymphopenia: Alefacept induces dose-dependent reductions in circulating CD4+ and CD8+ T-lymphocyte counts. Alefacept should not be initiated in patients with CD4+ T-lymphocyte count below normal. CD4+ T-lymphocyte counts should be monitored weekly throughout the course of the 12-week dosing regimen. Dosing should be withheld if CD4+ T-lymphocyte counts fall below 250 cells/μL. The drug should be discontinued if counts remain below 250 cells/μL for one month.

Malignancies: Alefacept may increase the risk of malignancies and should not be administered to patients with a history of systemic malignancy. Caution should be exercised when considering the use of alefacept in patients at high risk of malignancy and if malignancy develops during the course of alefacept therapy, the drug should be discontinued.

Serious Infections: Alefacept has the potential to increase the risk of infection and reactivate latent, chronic infections. It should not be administered to patients with a clinically important infection and caution should be exercised when considering the use of alefacept in patients with chronic infections or a history of recurrent infection. If a patient develops a serious infection during the course of alefacept therapy, the drug should be discontinued.

Drug Interactions

No formal drug interaction studies have been performed.

Efficacy Measures (Used in Clinical Trials)[3,5,6,7,8,9]

Psoriasis area-and-severity index score (PASI) - Based on a formulary encompassing lesion severity weighted by proportion of body surface area involved. PASI ranges from 0 (no disease) to 72 (very severe psoriasis involving entire body surface area).

Physician Global Assessment (PGA) - PGA uses the following 7-point scale:

Severe: Very marked plaque elevation, scaling or erythema.
Moderate-Severe: Marked plaque elevation, scaling or erythema.
Moderate: Moderate plaque elevation, scaling or erythema.
Mild-Moderate: Intermediate between moderate and mild.
Mild: Slight plaque elevation, scaling or erythema.
Almost clear: Intermediate between mild and clear.
Clear: No signs of psoriasis, postinflammatory hypopigmentation or hyperpigmentation.

Dermatology Life Quality Index (DLQI) – Ten-item questionnaire designed to assess the quality of life (QOL) of patients with a variety of skin conditions, including psoriasis. The DLQI assess daily activities, leisure

activities, impact on work or school, treatment-related distress, personal relationships, symptoms and feelings over the previous week. High scores represent worse QOL.

Dermatology Quality of Life Scales (DQOLS) – This instrument consists of 17 psychosocial items grouped into 4 categories, 12 activity items grouped into 4 categories and 12 symptom items. The DQOLS assess patients' current experience and higher scores indicate greater QOL impairment.

Short Form-36™ Health Survey (SF-36) – The SF-36 is a brief, general survey that assess health status in 8 multi-item scales, which are divided between 2 categories, i.e. role physical and role emotional. Higher SF-36 scores indicate a better QOL.

Clinical Trials[3,5,6,7,8,9]

Ellis CN, Krueger GG. Treatment of chronic plaque psoriasis by selective targeting of memory effector T-lymphocyes. *N Eng J Med* 2001;345:248-55.	
Objective:	To evaluate the use of alefacept as immunomodulatory therapy for psoriasis.
Subjects:	➤ Men (71%) & women 18-70 years with chronic plaque psoriasis diagnosed at least 12-months before screening and involving ≥ 10% BSA. ➤ Previously received systemic treatment or phototherapy, or candidates for such treatment. ➤ 81-91% with moderate-severe disease. ➤ Psoriasis area-and-severity index score (PASI) = 14-20, (PASIS: 0 = no psoriasis; 72 = most severe disease possible).
Methods:	➤ Phase II, randomized, double-blind, placebo-controlled, parallel group, multi-center trial. ➤ Four treatment arms: placebo (N=59), alefacept 0.025 mg/g (N=57), alefacept 0.075 mg/kg (N=55), alefacept 0.150 mg/kg (N=58). ➤ Study medication & placebo administered by IV injection once weekly x 12-weeks. ➤ Systemic treatments, phototherapy, potent topical medications not permitted from 4-weeks before study medication started until 2-weeks after completion. ➤ Subjects evaluated per PASI score and Physician Global Assessment (PGA) every 2-weeks during treatment phase and at weeks 1,2,4,8 & 12 during follow-up.
Results:	➤ 197/229 subjects (86%) received all 12 injections. ➤ 8% assigned to placebo discontinued treatment due to worsening psoriasis. ➤ 2% assigned to alefacept discontinued treatment due to worsening psoriasis. ➤ Decrease in PASI from baseline 2-weeks following completion of tx: • Placebo - 21% • Alefacept 0.025 mg/kg - 38% (P<0.001 vs. placebo) • Alefacept 0.075 mg/kg - 53% (P<0.001 vs. placebo) • Alefacept 0.150 mg/kg - 53% (P<0.001 vs. placebo) ➤ At least 50% reduction in PASI scores 2-weeks following completion of tx: • Placebo - 27% • Alefacept 0.025 mg/kg - 36% (P=0.001 vs. placebo) • Alefacept 0.075 mg/kg - 60% (P=0.001 vs. placebo) • Alefacept 0.150 mg/kg - 56% (P=0.001 vs. placebo) ➤ At least 50% reduction in PASI scores 12-weeks following completion of tx: • Placebo - 32% • Alefacept 0.025 mg/kg - 47% (P=0.02 vs. placebo) • Alefacept 0.075 mg/kg - 63% (P=0.02 vs. placebo) • Alefacept 0.150 mg/kg - 42% (P=0.02 vs. placebo) ➤ Subjects clear or "almost clear" of psoriasis 12-weeks following completion of tx (PGA): • Placebo - 0 (0%) • Alefacept - 28 (24%) ➤ Subjects treated with UV irradiation or systemic tx during post-treatment phase due to worsening symptoms: • Placebo - 11 (22%) • Alefacept - 11 (7.4%)
Safety:	➤ Side effects in which incidence in alefacept–treated pts exceeded incidence in placebo pts by ≥5%: • Accidental injury (unrelated to study protocol) • Dizziness • Nausea • Chills • Cough
Conclusion:	➤ Alefacept was an effective and well-tolerated treatment for chronic plaque psoriasis. ➤ Clinical improvement was sustained following the 12-week treatment period. ➤ The median interval between completion of study and re-treatment was 306 days. ➤ Alefacept is a new disease-remitting agent, which selectively reduces circulating CD450RO+ memory effector T-lymphocytes.

<table>
<tr><th colspan="2">Krueger GG, Ellis CN. Alefacept therapy produces remission for patients with chronic plaque psoriasis. Br J Dermatol 2003;148:784-88.</th></tr>
<tr><td>Objective:</td><td>To quantify the remission provided by alefacept, i.e. the time before patients required further alefacept therapy.</td></tr>
<tr><td>Methods:</td><td>➤ This open-label study assessed the remission period following alefacept therapy in subjects who participated in the Ellis and Krueger phase II trial of IV alefacept published in the N Eng J Med (see above for details regarding subjects and study design).

• Subjects who completed 12-week treatment and who were “clear” or “almost clear” per PGA at the end of the 12-week follow-up phase were eligible to receive subsequent courses of alefacept.
• Retreatment with alefacept initiated when disease progressed such that attending physician and patient agreed that systemic therapy was required.
• Time to re-treatment recorded as time from last dose of alefacept in phase II trial until further systemic therapy initiated.</td></tr>
<tr><td>Results:</td><td>➤ 28 subjects from phase II trial eligible, 26 participated in subsequent open-label study.

<table><tr><th colspan="2">Mean ± SD length of remission in three groups of alefacept-treated patients</th></tr><tr><th>Alefacept Dose (mg/kg)</th><th>Length of remission (days)</th></tr><tr><td>0.025 (n=8)</td><td>291 ± 108</td></tr><tr><td>0.075 (n=9)</td><td>338 ± 128</td></tr><tr><td>0.150 (n=9)</td><td>377 ± 92</td></tr></table>
➤ Patients did not require further systemic therapy with alefacept for a median of 10 months (range 6-18 mo).
➤ No correlation between dose of alefacept and length of remission.
➤ Additional courses of alefacept provided similar periods of remission.
➤ No reports of flares or rebound psoriasis after cessation of alefacept therapy.</td></tr>
<tr><td>Conclusion:</td><td>➤ Patients showed continued improvement following 12-week treatment course.
➤ Responses sustained without need for re-treatment with alefacept for up to 18-months.
➤ Durable responses with alefacept similar to those observed with PUVA therapy.</td></tr>
</table>

Krueger GG. Papp KA, Stough DB, et al. 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.

Objective: To further evaluate efficacy & tolerability of alefacept in a phase III study of patients with chronic plaque psoriasis.

Subjects:

- Men & women ≥16 years with chronic plaque psoriasis diagnosed at least 12-months before screening and involving ≥ 10% BSA.
  - 70% male.
  - Mean age 45 years
  - Median duration of psoriasis 18 years
  - Median BSA involvement = 22%.

Methods:

- Phase III, randomized, double-blind, placebo-controlled, parallel group, multi-center trial.
- Three treatment cohorts:
  - Cohort 1 - Two 12-week courses of alefacept 7.5 mg IV (n=183).
  - Cohort 2 - Alefacept 7.5 mg IV x 12-weeks followed by placebo x 12-weeks (n=184).
  - Cohort 3 - Placebo IV x 12-weeks followed by alefacept 7.5 mg IV x 12-weeks (n=186).
- Systemic treatments, phototherapy, potent topical medications prohibited within 4-weeks before and throughout study.
- Clinical response evaluated by PASI and PGA every 2-weeks during treatment and at all f/u visits.
- Primary efficacy end point: % of patients with ≥75% reduction in PASI at 2-weeks after last dose course #1.
- Other efficacy end points:
  - Overall response rate: Patients achieving "clear" or "almost clear" by PGA or ≥50%, or ≥75% reduction in PSAI any time during 12 week treatment period & 12-week follow-up period of either course.
  - "Clear" or "almost clear" by PGA 2-weeks after last dose in each course.
  - ≥50% reduction in PSAI 2-weeks after last dose in each course.
  - ≥75% reduction in PSAI 2-weeks after last dose in each course.
- Safety assessment: Adverse events, laboratory, physical exam.

Results:

- 482/553 (87.2%) completed course #1 & 401/482 (72.5%) completed course #2.

End point	Course 1* No. (%)		Course 2# (no. (%)		Both Courses, No. (%)
	Placebo (n=186)	Alefacept (n=367)	Placebo (n=142)	Alefacept (n=154)	Alefacept/Alefacept (n=183)
>75% PASI reduction					
2 wk after treatment	7 (4)	53 (14)[a]	10 (7)	36 (23)[a]	47 (26)
Overall response rate	15 (8)	102 (28)[a]	27 (19)	57 (37)[a]	73 (40)
>50% PASI reduction					
2 wk after treatment	18 (10)	139 (38)[a]	35 (25)	74 (48)[a]	100 (55)
Overall response rate	44 (24)	204 (56)[a]	70 (49)	99 (64)[b]	130 (71)
PGA "clear"/"almost clear"					
2 wk after treatment	7 (4)	42 (11)[b]	8 (6)	31 (20)[a]	39 (21)
Overall response rate	11 (6)	83 (23)[a]	25 (18)	46 (30)[b]	58 (32)

*Course 1: placebo (cohort 3); alefacept (cohorts 1 & 2)
#Course 2: placebo-controlled comparison, includes subjects in placebo (cohort 2) & alefacept (cohort 1) groups. Cohort 3 not included in analysis.
[a]P < 0.001 vs, placebo [b]P < 0.05 vs. placebo

- Course 1 – Max mean reduction from baseline PASI = 47% in combined alefacept group (cohorts 1 & 2).
- Maximal reduction occurred mean of 8-weeks after last dose.
- Two courses of alefacept (cohort 1) – Max mean reduction from baseline PASI = 54% at 6-weeks post treatment.
- Response to alefacept durable:
  - Single course – Duration 7-8 months
  - Two courses alefacept - ? duration, i.e. maintained ≥50% improvement at final study endpoint (48 weeks).

Safety:

Adverse Event	Course 1* No. (%)		Course 2# (no. (%)
	Placebo (n=186)	Alefacept (n=367)	Alefacept (n=153)
Accidental injury	30 (16)	73 (20)	28 (18)
Headache	38 (20)	62 (17)	18 (12)
Pharyngitis	23 (12)	52 (14)	20 (13)
Rhinitis	21 (11)	43 (12)	13 (8)
Pruritus	16 (9)	40 (11)	5 (3)
Chills	2 (1)	37 (10)	6 (4)
Flu syndrome	15 (8)	37 (10)	18 (12)
Infection	20 (11)	35 (10)	16 (10)

*Course 1: placebo (cohort 3); alefacept (cohorts 1 & 2)
#Course 2: alefacept (cohort 3)

Conclusion:

- 1or 2 courses of alefacept sig alleviated psoriasis & produced durable remission without rebound after tx cessation.
- Incremental effectiveness of a second alefacept course provides strong support for intermittent tx.
- Predict that alefacept will help meet unmet need for safe & effective remittive tx.

Lebwohl M, Christophers E, Langley R, et al. 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.

Objective:

To confirm and extend efficacy and tolerability profile for IM alefacept in patients with moderate-severe chronic plaque psoriasis.

Subjects:

➤ Men & women ≥18 years with chronic plaque psoriasis diagnosed at least 12-months before screening and involving ≥ 10% BSA.
- 66% male.
- 90% Caucasian
- Mean age 45 years
- Median duration of psoriasis 19 years
- Median pretreatment PASI = 14.2
- Median BSA involvement = 21%.

Methods:

➤ Phase III, randomized, double-blind, placebo-controlled, parallel group, multi-center trial.
➤ Three 12-week treatment arms followed by 12-week post-treatment observation period:
- Placebo IM once weekly x 12-weeks (n=168).
- Alefacept 10 mg IM once weekly x 12-weeks (n=173).
- Alefacept 15 mg IM once weekly x 12-weeks (n=166).

➤ Stratified by baseline PASI (> 20 or ≤ 20) & prior systemic or phototherapy.
➤ Systemic treatments, phototherapy, potent topical medications prohibited within 4-weeks before and throughout study.
➤ Clinical response evaluated by PASI and PGA every 2-weeks during treatment and at all f/u visits.
➤ Primary efficacy end point: Mean % change from baseline PASI.
➤ Other efficacy end points:
- Overall response rate: % of patients achieving ≥50%, or ≥75% reduction in PSAI and PGA of "clear" or "almost clear" any time during 12 week treatment period & 12-week follow-up period.

➤ Safety assessment: Adverse events, laboratory, physical exam.

Results:

➤ 142/168 (85%) of placebo and 303/339 (89%) of alefacept subjects completed 12-week treatment period.

➤ Mean reductions in PASI for all treatment groups reached maximum at 6-weeks postdosing:
- Placebo - 25%
- Alefacept 10 mg - 41%
- Alefacept 15 mg - 46%

➤ At least 75% reduction in PASI from baseline throughout study period:
- Placebo - 13%
- Alefacept 10 mg IM - 28% (P < 0.001 vs. placebo)
- Alefacept 15 mg IM - 33% (P < 0.001 vs. placebo).

(Of subjects in 15 mg alefacept group who achieved ≥75% PASI reduction 2-weeks after last dose, 74% maintained ≥50% reduction in PASI during 12-week f/u period.)

➤ At least 50% reduction in PASI from baseline throughout study period:
- Placebo - 35%
- Alefacept 10 mg IM - 53% (P = 0.002 vs. placebo)
- Alefacept 15 mg IM - 57% (P < 0.001 vs. placebo)

(Of subjects in 15 mg alefacept group who achieved at least 50%, but less than 75% PASI reduction 2-weeks after last dose, 79% maintained ≥25% reduction in PASI during 12-week f/u period.)

➤ Overall response rate for PGA of "clear" or "almost clear":
- Placebo - 8%
- Alefacept 10 mg IM - 22% (P < 0.001 vs. placebo)
- Alefacept 15 mg IM - 24% (P < 0.001 vs. placebo)

➤ Other findings:
- Response rates slightly lower for subjects who received prior systemic therapy.
- Alefacept superior to placebo regardless of baseline disease severity.
- In alefacept groups, patients with more severe disease at baseline tended to have higher response rates.

Safety:

Adverse Event	Placebo (n=168)	Alefacept 10 mg (n=173)	Alefacept 15 mg (n=166)	Total Alefacept (n=339)
Headache	26 (15%)	34 (20%)	30 (18%)	64 (19%)
Pruritus	16 (10)	24 (14)	30 (18)	54 (16)
Infection	19 (11)	25 (14)	26 (16)	51 (15)
CD4+ count < 250/μL	0	1 (<1)	1 (<1)	2 (<1)
Pharyngitis	15 (9)	20 (12)	20 (12)	40 (12)
Accidental injury	19 (11)	22 (13)	16 (10)	38 (11)
Rhinitis	11 (7)	24 (14)	9 (5)	33 (10)
Asthenia	18 (11)	10 (6)	18 (11)	28 (8)

Conclusion:

➤ IM alefacept effectively improves psoriasis & produces durable remissions without compromising immune fxn.
➤ IM alefacept has favorable safety profile, with no evidence of opportunistic infections or malignancies.
➤ IM alefacept provides a safe, effective & convenient alternative to IV administration.

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.

Objective: To exam the effects of IM alefacept on quality of life (QOL) in a large population of patients with chronic plaque psoriasis.

Methods:

➤ This study evaluated the QOL of subjects who participated in the Lebwohl, Christophers, Langley, et al. study. See review for details regarding subjects and study design.

➤ QOL evaluated by:

- Dermatology Life Quality Index (DLQI) – primary QOL instrument.
- Dermatology Quality of Life Scales (DQOLS)
- Short Form-36 Health Survey (SF-36)

Results:

➤ DLQI:

Treatment	Adjusted Mean Change from Baseline in DLQI	
	2-weeks after last dose	12-weeks after last dose
Placebo	-2.7	-2.8
Alefacept 10 mg	-3.8[a]	-3.7[a]
Alefacept 15 mg	-4.9[b]	-4.1[a]

[a] p = NS vs. placebo
[b] p < 0.001 vs. placebo

➤ DQOLS:

Treatment	Adjusted Mean Change from Baseline in DQOLS (2-weeks after last dose)		
	Psychosocial	Activities	Symptoms
Placebo	-5.4	-3.5	-8.4
Alefacept 10 mg	-7.3[a]	-6.0[a]	-12.6[a]
Alefacept 15 mg	-10.6[c]	-9.5[b]	-17.5[b]

[a] p = NS vs. placebo
[b] p < 0.001 vs. placebo
[c] p = 0.004 vs. placebo

Treatment	Adjusted Mean Change from Baseline in DQOLS (12-weeks after last dose)		
	Psychosocial	Activities	Symptoms
Placebo	-5.1	-4.5	-6.3
Alefacept 10 mg	-5.3[a]	-5.4[a]	-7.8[a]
Alefacept 15 mg	-7.7[a]	-7.3[a]	-12[d]

[a] p = NS vs. placebo
[d] p = 0.012 vs. placebo

➤ SF-36:

Treatment	Adjusted Mean Change from Baseline in SF-36 (2-weeks after last dose)	
	Physical Component	Mental Component
Placebo	-0.32	-0.44
Alefacept 10 mg	+1.04[a]	+1.11[a]
Alefacept 15 mg	+1.63[e]	+1.74[e]

[a] p = NS vs. placebo
[e] p < 0.025 vs. placebo

- Adjusted Mean Change from Baseline in SF-36 at 12-weeks after last dose – Investigators only reported stat sig difference vs. placebo for alefacept 15 mg for physical component of SF-36 (p = 0.008).

Conclusion:

➤ Alefacept 15 mg IM q week x12-weeks sig improved health-related QOL as measured by DLQI, DQOLS & SF-36.

➤ Patients receiving alefacept 15 mg IM q week x12-weeks had QOL improvements on SF-36 scale scores even when baseline scores were high enough to indicate little room for improvement.

➤ Results of this QOL analysis suggest that routine use of ≥75% improvement in PASI as primary efficacy endpoint may be too stringent, excluding patients who experience significant enhancement in QOL.

Lowe NJ, Gonzalez J, Bagel J, et al. Repeat courses of intravenous alefacept in patients with chronic plaque psoriasis provide consistent safety and efficacy. *Int J Dermatol* 2003;42:224-30.	
Objective:	To determine the safety and tolerability of repeat course of IV alefacept in patients with chronic plaque psoriasis that participated in previous phase II studies of alefacept.
Subjects:	➢ Men & women who participated in previous phase II studies of alefacept. • Required to complete 12-week treatment and observation periods of phase II studies. Mean age = 45 years 66% males Median BSA involvement = 19-21% Median PASI score = 9.9-13.3 Baseline PGA was moderate or moderate-severe in 57-78% of cases (re-treatment courses 1,2, & 3)
Methods:	➢ Open-label, multicenter, re-treatment study. ➢ Eligible patients received alefacept 7.5 mg once weekly as a 30-second IV bolus for 12-weeks. ➢ Minimum 12-week washout period required after each treatment course. ➢ PASI and PGA used to evaluate efficacy.
Results (Interim):	➢ 170 patients evaluable in re-treatment course 1and 50 patients evaluable in re-treatment courses 1&2. ➢ Maximum mean reduction from baseline PASI: • First re-treatment course – 51% (6^{th} week post-treatment) • Second re-treatment course – 47% (2^{nd} week post treatment) ➢ At least 75% reduction in PASI score, first re-treatment course - 39% ➢ At least 50% reduction in PASI score, first re-treatment course - 66% ➢ Subjects achieving PGA of "clear or "almost clear", first re-treatment course – 29%
Safety (Interim):	➢ Most common adverse events, re-treatment course 1: Pharyngitis 13% Rhinitis 13% ➢ Most common adverse events, re-treatment course 2: Infection 7% Rhinitis 7% Common cold most frequent event coded to "infection".
Conclusion:	➢ Alefacept was well tolerated when used in repeat 12-week courses of treatment for chronic plaque psoriasis. ➢ Patients had either an equivalent clinical response or further improvement after second re-treatment course. ➢ Results suggest that alefacept is remittive vs. suppressive therapy. ➢ Alefacept selectively reduced memory T-cells, with relative sparing of naïve T-cells. ➢ Most common adverse events during re-treatment were pharyngitis, rhinitis and infection (common cold).

Acquisition Cost (Open market prices)

Alefacept 7.5 mg:
Single dose pack (NDC 59627-0020-02) - $408.52
Carton containing 4 dose packs (NDC 59627-0020-01) - $1,634.09
Alefacept 15 mg:
Single dose pack (NDC 59627-0021-04) - $580.69
Carton containing 4 dose packs (NDC 59627-0021-03) - $2,322.75

Cost Analysis

The following tables provide drug expenditure data for alefacept and other systemic, remittive psoriasis therapies.

No. of 12-week Courses	Alefacept Expenditures (per patient)	
	Alefacept 7.5 mg IV q week	Alefacept 15 mg IM q week
1	$4,902.27	$6,968.25
2	$ 9,804.54	$13,936.50

Cost Analysis, cont.

Drug Cost for VA Formulary Systemic Psoriasis Therapies	
Regimen	**Drug cost per patient treated***
Methoxsalen 0.6 mg/kg, 10-20 treatments over 4-8 weeks	$111.64 - $223.28
Cyclosporine 2.5 – 5.0 mg/kg/d x 12-weeks	$315.17
Methotrexate 7.5 – 25 mg/week x 12-weeks	$8.75 - $29.16
Acitretin 25 – 50 mg/d x 12-weeks	$512.40 - $1024.80

*Based on 70 kg patient

Conclusion

In phase II and III placebo-controlled trials, alefacept demonstrated statistically significant improvement in several clinical endpoints including PASI and PGA. Onset of response began approximately 8-weeks following initiation of therapy. With one course of IV therapy, the median duration of response was approximately 7-months based on the maintenance of a ≥50% reduction in PASI. The findings of a quality of life analysis in patients receiving IM alefacept were generally consistent with the clinical (PASI) results, however, statistically significant differences compared to placebo were not achieved for all items in the QOL instruments used. Alefacept was generally well tolerated, however, rare, but potentially serious adverse events (lymphopenia, infections, malignancies) are a concern and primarily related to the drugs' immunosuppressive mechanism of action. Published clinical trials have been limited to a maximum of two 12-week courses of therapy and therefore, safety data on the long-term use of alefacept is lacking. Lastly, the acquisition cost of alefacept is high relative to other disease remitting therapies (PUVA, cyclosporine, methotrexate, retinoids) and currently, there are no comparative or pharmacoeconomic data available.

At this time, alefacept cannot be recommended for National VA or VISN Formulary addition given the safety concerns and lack of long-term usage and comparative data. It is recommended that national non-formulary usage criteria be developed to insure appropriate patient selection, therapeutic monitoring and safety surveillance.

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Prepared by: Edward LaHaie, Pharm.D. VISN11
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