PRODUCT MONOGRAPH

AMEVIVE®

alefacept

Lyophilized powder for reconstitution

15 mg/0.5 mL reconstituted solution for intramuscular injection
7.5 mg/0.5 mL reconstituted solution for intravenous injection

Selective immunomodulating antipsoriatic agent

Astellas Pharma Canada, Inc.
625 Cochrane Drive
Markham, Ontario L3R 9R9

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Table of Contents

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intramuscular injection	Lyophilized powder for reconstitution / 15 mg per 0.5 mL	None *For a complete listing see Dosage Forms, Composition and Packaging section.*
Intravenous injection	Lyophilized powder for reconstitution / 7.5 mg per 0.5mL	

DESCRIPTION
AMEVIVE® (alefacept) is a recombinant 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, C_H2 and C_H3 domains) portion of human IgG_1. Alefacept is produced by recombinant DNA technology in a Chinese Hamster Ovary (CHO) mammalian cell expression system. The molecular weight of alefacept is 91.4 kilodaltons.

INDICATIONS AND CLINICAL USE
AMEVIVE® (alefacept) is indicated for:
- treatment of patients with moderate to severe chronic plaque psoriasis who are candidates for phototherapy or systemic therapy.

Summary of Clinical Studies (see also Part II, Clinical Trials)
The safety and efficacy of AMEVIVE® (alefacept) in psoriasis were evaluated in two randomized, double-blind, placebo-controlled phase III studies in 1060 adults. In both studies, patients had chronic plaque psoriasis for more than one year and a minimum body surface area involvement of 10% prior to study entry. The patients' ages ranged from 16 to 84 years.

Patients received a treatment consisting of weekly doses of either AMEVIVE or placebo over 12 weeks and were followed for an additional 12 weeks without treatment after dosing. The use of low-potency topical steroids was allowed, but concomitant phototherapy or systemic therapy was not allowed. Study 1 evaluated the efficacy and safety of one versus two 12-week courses of AMEVIVE 7.5 mg administered by intravenous (IV) bolus. A total of 553 patients received either two courses of AMEVIVE, one course of AMEVIVE followed by one course of placebo, or one course of placebo followed by one course of AMEVIVE.

In Study 2, which examined the safety and efficacy of two different doses of AMEVIVE, patients received either 10mg, 15mg, or placebo, administered weekly for 12 weeks by intramuscular injection. Results are presented below for the 15 mg dose versus placebo only since 15 mg IM once weekly is the recommended dose.

In both studies, one course was defined as a 12-week treatment of once weekly injection followed by a 12-week observation period.

Efficacy Results

In Study 1, a greater proportion of patients (14%) treated with AMEVIVE® (alefacept) compared with 4% of patients receiving placebo ($p < 0.001$), achieved PASI 75 or greater response two weeks after the last dose of Course 1. The proportion of patients who achieved PASI 50 or greater response was 38% of patients treated with AMEVIVE, compared to 10% who received placebo ($p < 0.001$). A PGA assessment of almost clear or clear was achieved in 11% of patients treated with AMEVIVE compared with 4% who received placebo ($p = 0.004$).

In Study 2, the proportion of patients achieving PASI 75 or greater response two weeks after the last dose in the AMEVIVE and placebo groups were 21% and 5% ($p < 0.001$), respectively. The proportion of patients achieving PASI 50 or greater was 42% and 18% in the AMEVIVE and placebo groups, respectively ($p < 0.001$). The response rates for PGA almost clear or clear were 14% and 5% in the AMEVIVE and placebo groups ($p = 0.006$), respectively.

Assessment of clinical response at any time during the course of treatment and follow-up in Study 1 demonstrated that 28% of patients treated with AMEVIVE achieved PASI 75 or greater compared with 8% for placebo ($p < 0.001$) and 56% of patients treated with AMEVIVE achieved PASI 50 at any time compared to 24% for placebo ($p < 0.001$). Also 23% of patients treated with AMEVIVE achieved PGA almost clear or clear at any time compared to 6% for placebo ($p < 0.001$).

Similarly in Study 2, 33% of patients treated with AMEVIVE achieved PASI 75 or greater at any time during treatment and follow-up compared to 13% for placebo ($p < 0.001$) and 57% of patients treated with AMEVIVE achieved PASI 50 or greater at any time compared to 35% for placebo ($p < 0.001$). Also 24% of patients treated with AMEVIVE achieved PGA almost clear or clear at any time compared to 8% for placebo ($p < 0.001$).

Assessment of clinical response with a second course of AMEVIVE is based upon the comparison between the 154 patients in Cohort 1 and the 142 patients in Cohort 2 of Study 1. Patients in Cohort 1 received AMEVIVE during both courses of treatment (AMEVIVE/AMEVIVE) while patients in Cohort 2 received AMEVIVE during the first course and placebo during the second course (AMEVIVE/placebo). At two weeks after the last dose of course 2, 23% of patients treated with AMEVIVE/AMEVIVE achieved PASI 75 or greater compared to 7% of patients who received AMEVIVE/placebo ($p < 0.001$), 48% of patients treated with AMEVIVE/AMEVIVE achieved PASI 50 or greater compared to 25% of patients who received AMEVIVE/placebo ($p < 0.001$) and 20% of patients treated with AMEVIVE/AMEVIVE achieved PGA almost clear or clear compared to 6% of patients who received AMEVIVE/placebo ($p = 0.006$). At any time during treatment and follow-up 37% of patients treated with AMEVIVE/AMEVIVE achieved PASI 75 or greater compared to 19% who received AMEVIVE/placebo ($p<0.001$), 64% of patients treated with AMEVIVE/AMEVIVE achieved PASI 50 or greater compared to 49% who received AMEVIVE/placebo ($p=0.002$) and 30% of patients treated with AMEVIVE/AMEVIVE achieved PGA almost clear or clear compared to 18% who received AMEVIVE/placebo ($p=0.011$).

In patients in Study 1 who were randomized to receive two courses of AMEVIVE, 71% achieved a reduction in PASI score of at least 50% from baseline and 40% achieved a reduction in PASI score of at least 75% from baseline at any time after the start of dosing.

Clinical responses were initially evident within six weeks after the first dose in both studies. Maximal clinical responses may be seen up to six weeks post-dosing. Return of disease activity following cessation of treatment was generally slow. A second course of therapy provided additional benefit.

In general, clinical responses to AMEVIVE were durable. Patients were followed for up to 36 weeks following the completion of dosing patients with AMEVIVE (Study 1, cohort 2). Patients achieving a 75% reduction in PASI following a single 12-week treatment of AMEVIVE maintained at least a 50% reduction in PASI for a median of over seven months (216 days).

Following repeat courses of therapy, median duration of response was generally longer than following a single course. Intermittent treatment with additional 12-week courses of AMEVIVE therapy has been demonstrated to be safe and effective. Courses were separated by at least a 12-week monitoring period (see Dosage and Administration).

Following cessation of treatment, no disease rebound or flaring occurred at any time in either study.

Beneficial effects on Quality of Life (QOL), as measured by the Dermatology Life Quality Index (DLQI), were evident in both phase III studies.

Geriatrics (> 60 years of age):
During clinical studies, no overall differences in safety or effectiveness were observed between patients aged >60 years and younger patients.

Pediatrics (< 16 years of age):
The safety and effectiveness of AMEVIVE® (alefacept) in children below the age of 16 years has not been studied. AMEVIVE should not be administered in these patients.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- AMEVIVE® (alefacept) should not be administered to patients infected with HIV. AMEVIVE® reduces CD4+ T lymphocyte counts, which might accelerate disease progression or increase complications of disease in these patients (*see Warnings and Precautions: General and Immune*).

WARNINGS AND PRECAUTIONS

General
AMEVIVE™ (alefacept) induces dose-dependent reductions in circulating CD4+ and CD8+ T lymphocyte counts. AMEVIVE should not be administered to patients with a baseline total lymphocyte or CD4+ T cell count below normal. Beginning two weeks after the first dose, the CD4+ T lymphocyte counts should be monitored every two weeks during dosing and continuing throughout the course of the 12-week dosing regimen to guide subsequent dosing. If the CD4+ T cell count falls below 250 cells/μL, subsequent doses of AMEVIVE should be withheld until the CD4+ T cell count increases to 250 cells/ μL or more. AMEVIVE should be permanently discontinued in patients if CD4+ T lymphocyte counts remain below 250 cells/μL for one month. Prior to initiating another course of therapy, it is recommended that patients have total lymphocyte and CD4+ T cell counts within the normal range (see Dosage and Administration). Patients who develop a new clinically significant infection while undergoing treatment with AMEVIVE should be clinically monitored closely. If a patient develops a severe infection, dosing should be discontinued until the infection is completely resolved (*see Warnings and Precautions: Immune*)

Patients should be informed that:
- AMEVIVE® (alefacept) needs to be administered under the guidance and supervision of a qualified health care professional.
- There is a need for regular monitoring of white blood cell (lymphoctye) counts during therapy and that results of this biweekly blood test should be confirmed *before* administration of subsequent injections.

- AMEVIVE reduces lymphocyte counts, which may increase their chances of developing an infection or malignancy. Patients should be advised to inform their physician if they develop an infection or malignancy while undergoing a course of therapy with AMEVIVE.

When a physician determines that AMEVIVE can be used outside of the physician's office, persons who will be administering AMEVIVE 15 mg IM should receive instruction in reconstitution and injection, including a review of the injection procedures. If a patient is to self-administer, the physical ability of the patient to self-inject IM should be assessed. If home use is chosen, the first IM injection should be performed under the supervision of a qualified healthcare professional. Patients should be instructed in the technique and importance of proper syringe and needle disposal and be cautioned against reuse of these items. A puncture resistant container for disposal of needles should be used (*see Part III Consumer Information*).

Carcinogenesis and Mutagenesis

AMEVIVE® (alefacept) may increase the risk of malignancies. Some patients who received AMEVIVE in clinical studies developed malignancies. The observed rates and incidences were similar to those expected for the population studied (*see Adverse Reactions: Malignancies*). In non-clinical studies, animals developed B cell hyperplasia and one animal developed a lymphoma. AMEVIVE should not be administered to patients with a history of systemic malignancy. Caution should be exercised when considering the use of AMEVIVE in patients at high risk for malignancy. If a patient develops a malignancy, AMEVIVE should be discontinued.

No carcinogenicity or fertility studies were conducted.

Mutagenicity studies were conducted *in vitro* and *in vivo*; no evidence of mutagenicity was observed.

Hepatic/Biliary/Pancreas

During post-marketing surveillance there have been reports of liver injury, including hepatitis, decompensation of cirrhosis and acute liver failure. Some cases were reported with concomitant alcohol use. The role of AMEVIVE® (alefacept) in these events has not been established. AMEVIVE should be discontinued in patients who develop clinical signs of liver injury.

Immune

AMEVIVE® (alefacept) has the potential to increase the risk of infection and may reactivate latent, chronic infections. AMEVIVE should not be administered to patients with a clinically important infection. Caution should be exercised when considering the use of AMEVIVE 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 AMEVIVE. New infections should be monitored closely. If a patient develops a serious infection, AMEVIVE should be discontinued (*see Adverse Reactions, Infections*).

During the clinical development of AMEVIVE, no generalised immunosuppressive effects were observed in psoriasis patients. In a controlled study (n=46), there was no evidence to suggest impaired antibody (IgM and IgG) responses either during or after alefacept therapy. The data from this study suggest that patients treated with AMEVIVE mounted a normal antibody response to the tetanus toxoid (recall antigen) and to an experimental neo-antigen. The safety and efficacy of live or live-attenuated vaccines administered to patients being treated with AMEVIVE is unknown.

Patients were tested at multiple time points for antibodies to AMEVIVE. Low titers of antibodies to AMEVIVE were detected in sera of less than 3% of psoriasis patients receiving AMEVIVE. No apparent correlation between antibody development and clinical response or adverse events was observed. The long-term immunogenicity of AMEVIVE is unknown.

The data reflect the percentage of patients whose test results were considered positive for antibodies to alefacept in an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications and underlying disease.

Sensitivity/Resistance

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

Special Populations

Pregnant Women: There were no abortifacient or teratogenic effects in pregnant non-human primates. No evidence of fetal toxicity, malformations, or adverse effects on growth or development was observed in any of these animals. Trans-placental passage was observed.

No studies were conducted in pregnant women. Patients planning to become pregnant should not be treated with AMEVIVE® (alefacept). If pregnancy inadvertently occurs during treatment, discontinuation of AMEVIVE is recommended. Women of child-bearing potential receiving AMEVIVE should be advised to take adequate contraceptive measures. It is not known if AMEVIVE alters the efficacy of oral contraceptives.

Data on a limited number (2) of exposed pregnancies indicate no adverse effect of AMEVIVE on pregnancy or on the health of the fetus or newborn child.

Nursing Women:

It is not known whether AMEVIVE is excreted in human milk. Treatment with AMEVIVE should be avoided while nursing.

Pediatrics (< 16 years of age):
The safety and effectiveness of AMEVIVE® (alefacept) in children below the age of 16 years have not been studied. AMEVIVE should not be administered to these patients.

Geriatrics (> 60 years of age):
Of the 1357 patients who received AMEVIVE® (alefacept) in clinical studies, a total of 135 psoriasis patients aged 60-69 years and a total of 30 patients age >69 years have been treated with AMEVIVE. No overall differences in safety or effectiveness were observed between these patients and younger patients.

Monitoring and Laboratory Tests
CD4+ T lymphocyte counts should be monitored every two weeks during the 12-week dosing period and used to guide dosing. Patients should have normal CD4+ T lymphocyte counts prior to an initial or a subsequent course of treatment with AMEVIVE® (alefacept). Dosing should be withheld if CD4+ T lymphocyte counts are below 250 cells/μL. AMEVIVE should be discontinued if CD4+ T lymphocyte counts remain below 250 cells/μL for one month.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Events Leading to Discontinuation of Treatment
The proportion of patients who discontinued treatment due to adverse events was approximately 2% of patients treated with AMEVIVE® (alefacept) and 1% of placebo-treated patients. The most frequent adverse events leading to discontinuation in patients treated with AMEVIVE included headache and nausea. Infections leading to discontinuation included isolated cases of pneumonia and herpes zoster.

In Study 1, 10% of patients temporarily discontinued treatment and 2% permanently discontinued treatment due to CD4+ T cell counts below the specified threshold of 250 cells/μL. In Study 2, 4% temporarily discontinued treatment and none permanently discontinued treatment due to CD4+ counts below the specified threshold of 250 cells/μL.

Effects on Liver Function
In placebo-controlled studies, elevations of liver function tests were observed at a similar rate of incidence in placebo and patients treated with AMEVIVE® (alefacept) following single or repeated courses of treatment. Rare cases of elevations of transaminases to 5-10 times the upper limit of normal without associated hyperbilirubinemia were observed in both patients treated with AMEVIVE and placebo.

During post-marketing surveillance rare hepatic events, including a case of hepatitis associated with transient coagulopathy and hyperbilirubinemia, have been reported.

Injection Site Reactions

In Study 2, 16% of patients treated with AMEVIVE® (alefacept) and 8% of placebo-treated patients reported injection site reactions. Reactions at the site of injection were generally mild, typically occurred on single occasions, and included either pain (7%), inflammation (4%), bleeding (4%), edema (2%), non-specific reaction (2%), mass (1%), or skin hypersensitivity (<1%). During clinical trials, there was only one case of injection site reaction leading to the discontinuation of AMEVIVE.

Effect on Lymphocyte Levels

Overall in the first course of Studies 1 and 2, the mean total lymphocyte, CD4+ and CD8+ T cell counts remained above the lower limit of normal (LLN) throughout the 12 weeks of dosing and 12 weeks of follow-up. The maximal effects on lymphocytes were observed within 6 to 8 weeks of initiation of treatment with a rise in mean counts on cessation of treatment. Recovery rates varied between individuals with the majority of recovery occurring immediately in the 12 weeks following cessation of dosing. Table 1 provides the proportion of patients who experienced a maximal reduction in lymphocytes below the LLN and those who, within the period of observation (12 weeks post dosing), had lymphocyte counts below the LLN. In both studies 1 and 2, there was no evidence of predisposition to infections in patients with a low total lymphocyte count (see Precautions: Serious Infections).

Table 1.: Lymphocyte, CD4+ and CD8+ counts in patients treated with AMEVIVE

Lymphocyte parameters	**Study 1**	**Study 2**
Total Lymphocytes		
mean count at baseline	2089	2159
patients < LLN at time of maximum reduction	18%	9%
mean count at time of maximum reduction	1236	1384
patients <LLN at 12 weeks post dosing	4%	2%
mean count at 12 weeks post dosing (cells/µL)	1724	1841
CD4+ T cells		
mean count at baseline	901	909
patients < LLN at time of maximum reduction	46%	31%
mean count at time of maximum reduction	459	542
patients <LLN at 12 weeks post dosing	19%	7%
mean count at 12 weeks post dosing (cells/µL)	634	745
CD8+ T cells		
mean count at baseline	495	508
patients < LLN at time of maximum reduction	58%	46%
mean count at time of maximum reduction	231	269
patients <LLN at 12 weeks post dosing	36%	22%
mean count at 12 weeks post dosing (cells/µL)	336	396

LLN: Total lymphocytes 910 cells/µL; CD4+ 404 cells/µL; CD8+ 220 cells/µL

Infections

In the first course of placebo-controlled studies, adverse events considered as infections were reported in a total of 176 patients (43%) following placebo and 393 patients (45%) following AMEVIVE® (alefacept). Infections reported at an incidence of 5% or greater in the first course of therapy were pharyngitis, flu syndrome, nasopharyngitis (common cold), and viral infection. The incidence of infection did not increase with subsequent courses of therapy.

In the first course of placebo-controlled studies, infections requiring hospitalization were seen at a rate of less than 1%, similar to that of the placebo group. The nature of infections reported was similar to the nature of infections reported in the placebo-treated patients. In patients receiving repeated courses of therapy, the rates were 1% and 2% in the second and third course of therapy respectively. Infections requiring hospitalization included cellulitis, abscess, post-operative and burn wound infection, appendicitis, cholecystitis, gastroenteritis, toxic shock, and pneumonia. In general these infections occurred in patients with pre-existing risk factors. No opportunistic infections were reported.

Malignancies

In the 24-week period constituting the first course of placebo-controlled studies, 13 malignancies were diagnosed in 11 patients treated with AMEVIVE® (alefacept). The incidence of malignancies was 1.3% (11/876) for patients treated with AMEVIVE compared to 0.5% (2/413) in the placebo group.

During clinical development the most common malignancy in patients treated with AMEVIVE was squamous cell and basal cell cancers of the skin. Most of the patients had pre-existing risk factors such as PUVA/UVB exposure. In placebo-controlled clinical studies skin carcinoma was observed in 0.7% (6/876) of patients treated with AMEVIVE and 0.2% (1/413) of placebo-treated patients. Uncommon cases of lymphoma (non-Hodgkin's follicular cell lymphoma and Hodgkin's disease) have also been observed. The incidence of lymphoid malignancies was consistent with that expected in the moderate to severe psoriasis population. The role of AMEVIVE in the development of lymphoid malignancies is unknown.

The observed rates and incidences were similar to those expected for the population studied (see Precautions).

Hypersensitivity Reactions

In clinical studies, two patients were reported to experience angioedema, one of whom was hospitalized. In the 24-week period constituting the first course of placebo-controlled studies, urticaria was reported in <1% (6/876) patients treated with AMEVIVE® (alefacept) vs. 1 of 413 patients in the control group. Urticaria resulted in discontinuation of therapy in one of the patients treated with AMEVIVE.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

AMEVIVE® (alefacept) has been studied in 1357 psoriasis patients who received at least one course of AMEVIVE, of whom 876 patients received their first course in placebo-controlled studies. Ages ranged from 16 to 84 years with a mean age of 45 years; 69% were males and 31% were females.

Table 2. - Incidence of Adverse Events Experienced in at Least 5% of Patients in the First Course of AMEVIVE in Placebo-Controlled Studies

	AMEVIVE n= 876 (%)	**Placebo n= 413 (%)**
# patients with an event	730 (83%)	327 (79%)
Headache	17	18
Accidental Injury	15	13
Pharyngitis	15	13
Infection	11	11
Pruritis	11	8
Rhinitis	11	10
Flu syndrome	9	9
Viral infection	6	7
Asthenia	6	7
Chills	6	1
Pain	6	5
Diarrhea	5	5
Dizziness	5	3
Arthralgia	5	6
Nausea	5	3

Table 2 shows the incidence of adverse events experienced in at least 5% of patients in the first course of treatment in placebo-controlled studies. Adverse events overall were similar to placebo. Chills was the only event seen at an incidence of 5% or greater in AMEVIVE versus placebo-treated patients. Chills were most frequently observed within 24 hours of dosing when AMEVIVE was administered intravenously. Chills were mild to moderate severity and were not dose limiting.

Multiple Course Experience

In clinical studies, 346 patients received at least two courses, 125 patients received at least three courses, and 56 patients received at least four courses of AMEVIVE® (alefacept) administered intravenously over a period of up to two years. The safety experience in those patients that received multiple courses of therapy was similar to that observed in patients that received a single course.

The incidence of adverse events experienced in at least 5% of patients receiving multiple courses of AMEVIVE include headache, pharyngitis, accidental injury, rhinitis, infection, flu-syndrome, pruritus, chills, asthenia, pain, diarrhea, nausea, viral infection, dizziness, and sinusitis.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

In the first course of placebo-controlled studies, adverse events requiring hospitalization were observed at a rate of 5% in both patients treated with AMEVIVE™ (alefacept) and placebo-treated patients. The rate of occurrence of these events did not increase with subsequent courses of treatment. The most commonly reported adverse events requiring hospitalization in patients treated with AMEVIVE were cardiovascular events including coronary artery disease, myocardial infarction, chest pain, atrial fibrillation, complete atrio-ventricular block, and congestive heart failure. These events were infrequent and were generally observed in patients with pre-existing risk factors.

Other less common events (incidence of at least 1%) that were observed at a higher rate in patients treated with AMEVIVE in comparison with placebo are listed below by body system.

Body as a whole: back pain, abdominal pain, fever, malaise, chest pain.
Cardiovascular: hypertension.
Digestive: tooth disorder, periodontal abscess, vomiting.
Musculoskeletal: myalgia, arthritis.
Nervous System: anxiety, hypertonia, paresthesis, somnolence.
Respiratory: increased cough, asthma.
Skin and appendages: rash, herpes simplex, acne, benign skin neoplasm, contact dermititis.
Special Senses: conjunctivitis.
Urogenital: vaginal moniliasis.

Use with Other Psoriasis Therapies

The safety profile of AMEVIVE ® (alefacept) was evaluated when used in combination with

other psoriasis treatments. In two studies involving 261 patients AMEVIVE 15 mg once weekly for 12 weeks was used both alone (n=116) or in combination with either UVB (n=49) or cyclosporine (n=16) or methotrexate (n=21) or systemic retinoids (n=10), or mid- to high-potency topical treatments (n=48). The incidence of adverse events was similar in all the patient groups that received combination therapies. The safety profile was demonstrated to be similar to that observed in the phase III clinical trials in terms of the types and frequencies of adverse events, indicating that AMEVIVE, in combination with other psoriasis treatments, was well tolerated. The most common adverse events were headache (12%) and nasopharyngitis(8%).

In both studies, there were no reports of opportunistic infection nor was there an increased risk of infection or malignancy observed. Three patients had non-serious skin malignancies diagnosed. One patient receiving AMEVIVE alone had both a squamous cell and a basal cell carcinoma, one patient receiving AMEVIVE with 12 weeks UVB experienced a basal cell carcinoma and one patient receiving AMEVIVE with cyclosporine experienced a squamous cell carcinoma. During the dosing period at the time of maximal reduction in circulating CD4 T-cell counts no significant differences were observed between those patients receiving AMEVIVE alone or those patients receiving AMEVIVE in combination with the other psoriasis treatments. The clinical correlation and significance of these results require further assessment.

DRUG INTERACTIONS

Overview

No formal drug interaction studies have been conducted with AMEVIVE® (alefacept). Topical medications such as topical steroids and emollients can be used concomitantly with AMEVIVE.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- AMEVIVE® (alefacept) is intended for use under the guidance and supervision of a health care professional.
- Patients may self-inject the intramuscular injection only if their physician determines that it is appropriate and with medical follow-up, as necessary, after proper training in IM injection technique.
- Total lymphocyte and CD4+ T lymphocyte counts should be normal prior to initiating treatment with AMEVIVE. CD4+ T lymphocyte counts should be monitored every two weeks during the 12-week dosing regimen. Dosing should be withheld if CD4+ T lymphocyte counts are below 250 cells/μL. AMEVIVE should be discontinued if the counts remain below 250 cells/μL for one month *(see Warnings and Precautions, Monitoring and Laboratory Tests).*

Recommended Dose and Dosage Adjustment

- 15 mg given once weekly as an intramuscular injection OR
- 7.5 mg given once weekly as an intravenous bolus.

The recommended regimen is a course of up to 12 injections over a 12-week period. Intermittent re-treatment with subsequent courses may be initiated as needed provided that total lymphocyte and CD4+ T cell counts are within the normal range and a minimum of a 12-week interval has passed between courses of treatment.

Missed Dose

If you forget to take a dose on the day it is scheduled, you should contact your doctor.

Administration

AMEVIVE® (alefacept) must be reconstituted with supplied sterile Water for Injection using aseptic technique prior to intramuscular or intravenous administration.

Reconstitution:

Parenteral Products:

Vial Size	Volume of Water for Injection to be used for reconstitution	Available Volume	Nominal Concentration per 0.5 mL
15 mg for intramuscular administration	0.6 mL	0.5 mL	15 mg
7.5 mg for direct intravenous injection	0.6 mL	0.5 mL	7.5 mg

During reconstitution of AMEVIVE, inject the sterile Water for Injection very slowly into the vial, keeping the needle pointed at the sidewall of the vial. Some foaming will occur, which is normal. To avoid excessive foaming, do not shake or vigorously agitate. The contents should be swirled gently during dissolution. Generally, dissolution of AMEVIVE takes less than two minutes.

The reconstituted solution should be clear and colourless to slightly yellow and used as soon as possible after reconstitution. Visually inspect the solution for particulate matter and discolouration prior to administration. The solution should not be used if discoloured or cloudy, or if particulate matter remains.

Remove the needle used for reconstitution and attach the other supplied needle. Withdraw the solution into the syringe, removing only 0.5 mL from the vial. Some foam or bubbles may remain in the vial.

Do not add other medications to solutions containing AMEVIVE. Do not reconstitute AMEVIVE with other diluents. Do not filter reconstituted solution during preparation or administration.

Once reconstituted, the solution should be used immediately.

For intramuscular use, inject the full 0.5 mL of solution. Rotate injection sites so that a different site is used for each new injection. New injections should be given at least 1 inch from an old site and never into areas where the skin is tender, bruised, red or hard.

For intravenous use,

- Prepare 2 syringes with 3.0 mL Normal saline, USP for pre- and post-administration flush.
- Prime the winged infusion set with 3.0 mL saline and insert the set into the vein.
- Attach the AMEVIVE-filled syringe to the infusion set and administer the solution over no more than 5 seconds.
- Flush the infusion set with 3.0 mL saline, USP.

OVERDOSAGE

The highest dose tested in humans (up to 0.75 mg/kg IV) were associated with chills, headache, arthralgia and sinusitis. Patients inadvertently administered in excess of the recommended dose should be monitored for effects on total lymphocyte count and CD4+ T cell count.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

AMEVIVE ® (alefacept) exerts its effect via a dual mechanism of action. Chronic plaque psoriasis is a T cell mediated disorder that is characterized by the presence of memory-effector T cells (CD45RO+) in skin lesions. The majority of T cells express activation markers (CD2, CD25, CD69) and release inflammatory cytokines (IFNγ). T lymphocyte activation includes an interaction between LFA-3 on antigen presenting cells (APC) and CD2 on T lymphocytes. AMEVIVE prevents T cell activation by specifically binding to CD2 on the T-cell thereby inhibiting the interaction between CD2 on the T-cell and LFA-3 on the Antigen Presenting Cell. In addition, the Fc portion of AMEVIVE binds to Fc gamma receptors on cytotoxic cells, such as natural killer cells, leading to apoptosis of CD2+ target T cells. AMEVIVE selectively targets T cells that express high levels of CD2, such as activated and memory-effector T cells.

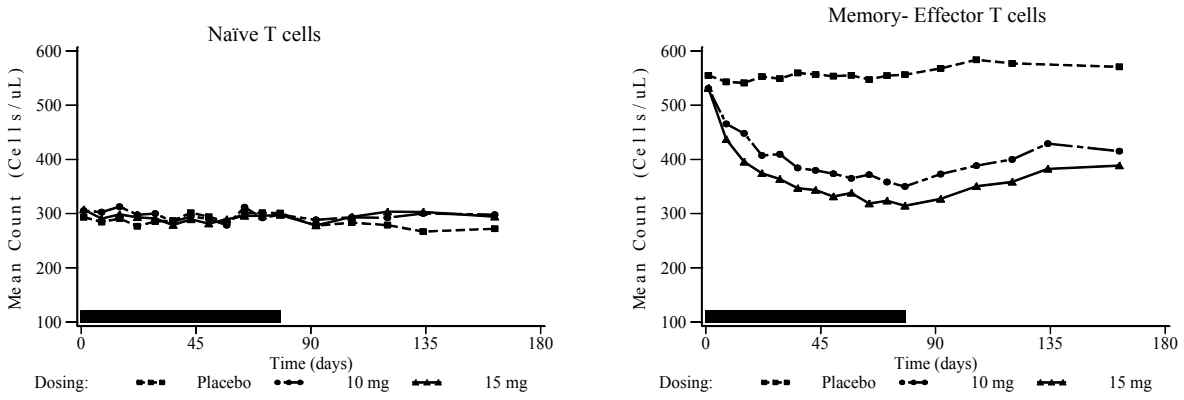
In vivo, exposure to AMEVIVE is associated with reductions in the number of circulating activated CD25+, CD4+CD45RO+, and CD8+CD45RO+ memory-effector T cells, detectable as a reduced total lymphocyte, CD4+, or CD8+ T cell count. Repeat courses of alefacept induce effects that are similar on circulating total lymphocytes as those seen following one course of therapy.

CD4+ and CD8+ T cells are the predominant phenotype within the psoriatic lesions. The reduction of CD4+CD45RO+ and CD8+CD45RO+ memory T cells is correlated with clinical outcome after the administration of AMEVIVE to psoriatic patients. Patients with a >50% reduction in Psoriasis Area Severity Index (PASI) score had a significant reduction in intra-lesional lymphocytes, particularly IFNγ-secreting T cells.

Pharmacodynamics

Therapy with AMEVIVE™ (alefacept) results in dose-dependent decreases in circulating total lymphocyte, CD4+, and CD8+ T cell counts. AMEVIVE does not cause general immunosuppresion. Rather, AMEVIVE exhibits specificity against CD4+CD45RO+ and CD8+CD45RO+ memory-effector T cells (see Figure 1). Naïve T cells (CD4+CD45RA+ and CD8+CD45RA+), B cells, and natural killer cells do not demonstrate significant changes in circulating levels during single or multiple courses of AMEVIVE therapy. Reductions in lymphocyte counts could occur in the first six weeks of therapy.

Figure 1: Effect of AMEVIVE on Naïve and Memory-Effector T Cells



*Solid bar indicates dosing interval

Pharmacokinetics

The pharmacokinetics of AMEVIVE® (alefacept) have been evaluated following both single and repeat dosing by intravenous (IV) and intramuscular (IM) routes of administration. Following repeat dosing to psoriasis patients, the disposition of AMEVIVE was consistent following IV and IM dosing. The bioavailability of AMEVIVE following IM administration in healthy volunteer studies was approximately 63%.

Table 3. Pharmacokinetic parameters of AMEVIVE following repeat-dosing to psoriasis patients

	Mean elimination $t_{½}$ (h)	Mean clearance (mL/h/kg)	Mean volume of distribution (mL/kg)
15 mg IM injection n=166	270	0.46*	167*
7.5 mg IV injection n=520	267	0.25	94

* Unadjusted for bioavailability

Special Populations and Conditions

Pediatrics and Geriatrics: The pharmacokinetics of AMEVIVE® (alefacept) in children and the elderly have not been studied.

Gender or Race: No differences in pharmacokinetics have been observed as a function of gender or ethnicity.

Hepatic or Renal Insufficiency: Effects on the pharmacokinetics of AMEVIVE have not been studied.

Duration of Effect

Duration of effect represents the maximum period of response. In general, clinical responses to AMEVIVE™ (alefacept) were durable. Patients were followed for up to 36 weeks following the completion of dosing patients with AMEVIVE (Study 1, cohort 2). Patients achieving a 75% reduction in PASI following a single 12-week treatment of AMEVIVE maintained at least a 50% reduction in PASI for a median of over seven months (216 days).

This remittive and sustained effectiveness was also observed with patients who reached a PGA of 'almost clear' or 'clear'. A prolonged effect of at least a 50% reduction in PASI for a median of eight months (241 days) was maintained in these patients.

Following repeat courses of therapy, median duration of response was generally longer than following a single course. Intermittent treatment with additional 12-week courses of AMEVIVE therapy has been demonstrated to be safe and effective. Courses were separated by at least a 12-week monitoring period *(see Dosage and Administration).*

Following cessation of treatment, no disease rebound or flaring occurred at any time in either study.

STORAGE AND STABILITY

Do not use a dose administration pack beyond the expiry date stamped on the carton, dose tray label, vial label, or diluent container label. The dose administration pack containing AMEVIVE® (alefacept) lyophilized powder must be stored in the refrigerator (2°C to 8°C).

If refrigeration is unavailable, AMEVIVE can be stored at temperatures up to 30°C for up to 48 hours.

Once reconstituted, the solution should be used immediately. If not administered immediately after reconstitution, AMEVIVE may be stored in the vial for up to 4 hours if refrigerated at 2°C to 8°C. ANY AMEVIVE NOT USED WITHIN 4 HOURS OF RECONSTITUTION SHOULD BE DISCARDED.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Intramuscular administration

Each dose pack contains one 15-mg single-use vial of AMEVIVE, one single-use 10 mL sterile Water for Injection vial, one syringe, two needles, two alcohol prep pads, one gauze pad, and one bandage. Supplied in cartons of one or four dose administration packs.

Each 15-mg single-use vial of AMEVIVE contains :
15 mg alefacept
12.5 mg sucrose
5.0 mg glycine
3.6 mg sodium citrate dihydrate
0.06 mg citric acid monohydrate

Intravenous administration

Each dose pack contains one 7.5-mg single-use vial of AMEVIVE, one single-use 10 mL sterile Water for Injection vial, one syringe, two needles, two alcohol prep pads, one gauze pad, and one bandage and one winged infusion set. Supplied in either one or four dose administration packs.

Each 7.5-mg single-use vial of AMEVIVE contains:
7.5 mg alefacept
12.5 mg sucrose
5.0 mg glycine
3.6 mg sodium citrate dihydrate
0.06 mg citric acid monohydrate

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: alefacept (USAN)

Chemical name: alefacept (USAN)

Molecular formula and molecular mass: 91.4 kilodaltons

Structural formula: Recombinant 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.

Physicochemical properties: The reconstituted solution has a pH of approximately 6.9.

Product Characteristics

Supplied as a sterile, white to off-white, preservative-free, lyophilized powder for parenteral administration. After reconstitution with 0.6 mL of the supplied sterile Water for Injection, USP, preservative-free, the solution of AMEVIVE is clear, colourless to slightly yellow.

CLINICAL TRIALS

Study demographics and trial design

The safety and efficacy of AMEVIVE™ (alefacept) in psoriasis were evaluated in two randomized, double-blind, placebo-controlled phase III studies in 1060 adults. In both studies, patients had chronic plaque psoriasis for more than one year and a minimum body surface area involvement of 10% prior to study entry. The patients' ages ranged from 16 to 84 years. Patients received a treatment consisting of weekly doses of either AMEVIVE or placebo over 12 weeks and were followed for an additional 12 weeks without treatment after dosing. The use of low- potency topical steroids was allowed, but concomitant phototherapy or systemic therapy was not allowed.

Table 4.- Summary of patient demographics for clinical trials in specific indication

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)
1	Randomized, double-blind, placebo-controlled. 12 weekly doses of either 7.5 mg IV AMEVIVE or placebo followed by 12 weeks without treatment.	AMEVIVE/ AMEVIVE (Cohort 1)	183 / 154
		AMEVIVE / placebo (Cohort 2)	184 / 142
		Placebo / AMEVIVE (Cohort 3)	186 / 153
2	Randomized, double-blind, placebo-controlled. 12 weekly doses of either AMEVIVE or placebo followed by 12 weeks without treatment.	10 mg IM AMEVIVE[a]	173
		15 mg IM AMEVIVE	166
		Placebo	168

In both studies, one course was defined as a 12-week treatment of once weekly injection followed by a 12-week observation period.

Study results

The primary efficacy endpoint in both studies was the proportion of patients with a reduction in score on the Psoriasis Area and Severity Index (PASI) of at least 75% from baseline two weeks post-treatment (in Study 1, this applied to Course 1). Additional efficacy measures based on PASI and Physician's Global Assessment (PGA) were evaluated two weeks post-treatment, or at

[a] Results are presented for the 15 mg dose versus placebo only since 15 mg IM once weekly is the recommended dose.

any time during a course of treatment. Efficacy outcomes are shown in Table 5 and 6 for Studies 1 and 2, respectively.

For patients in the third cohort, who received one course of placebo followed by one course of AMEVIVE® (alefacept), the following results were obtained: 16% achieved the primary endpoint of ≥ 75% reduction from baseline PASI, 39% achieved ≥ 50% reduction from baseline PASI and 12% reached a PGA of "almost clear or clear" at 2 weeks post-treatment following one course, and 28%, 52% and 22% achieved the same endpoints at any time after the first dose. Overall, these results are consistent with those that have been seen with the first cohort.

Table 5.- Efficacy endpoints based on proportions of patients responding by course in Study 1

	Course 1			Course 2			Over 2 Courses
	Placebo n=186	AMEVIVE 7.5 mg n=367[1]	p value	Placebo n=142[2]	AMEVIVE 7.5 mg n=154[3]	p value	AMEVIVE 7.5 mg/ AMEVIVE 7.5 mg n=183
Endpoints at 2 weeks after the last dose							
≥75% reduction from baseline PASI	4%	14%	p<0.001	7%	23%	p<0.001	26%
≥50% reduction from baseline PASI	10%	38%	p<0.001	25%	48%	p<0.001	55%
PGA almost clear or clear	4%	11%	p=0.004	6%	20%	p=0.006	21%
Endpoints at any time during treatment and follow-up							
≥75% reduction from baseline PASI	8%	28%	p<0.001	19%	37%	p<0.001	40%
≥50% reduction from baseline PASI	24%	56%	p<0.001	49%	64%	p=0.002	71%
PGA almost clear or clear	6%	23%	p<0.001	18%	30%	p=0.011	32%

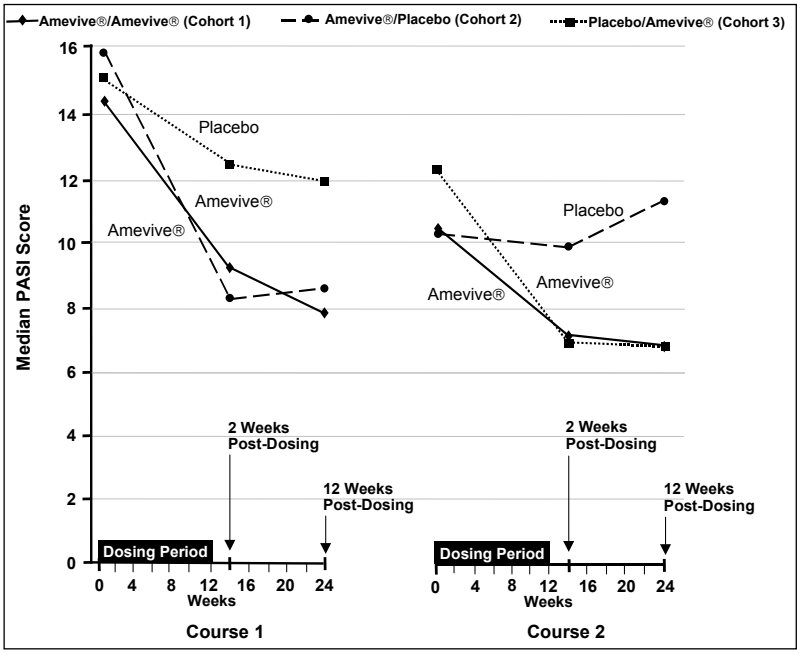
Note: p values: AMEVIVE 7.5mg vs placebo
PGA= Physician Global Assessment; PASI= Psoriasis Area Severity Index
[1] Cohorts 1 and 2 are combined.
[2] Patients included in this placebo group received AMEVIVE in the first course of therapy (Cohort 2).
[3] Patients included in this group received AMEVIVE in the first course of therapy (Cohort 1). Cohort 3 was not included in this analysis.

Table 6. Efficacy Endpoints Based on Proportions of Patients Responding in Study 2

	Study 2		
	Placebo n=142	AMEVIVE 15 mg n=166	p value
Endpoints at 2 weeks after the last dose			
≥75% reduction from baseline PASI	5%	21%	p<0.001
≥50% reduction from baseline PASI	18%	42%	p<0.001
PGA almost clear or clear	5%	14%	p=0.006
Endpoints at any time during treatment and follow-up			
≥75% reduction from baseline PASI	13%	33%	p<0.001
≥50% reduction from baseline PASI	35%	57%	p<0.001
PGA almost clear or clear	8%	24%	p<0.001

The change in PASI scores over the two courses of treatment in Study 1 is displayed in Figure 2.

Figure 2: Reduction in PASI scores in Study 1

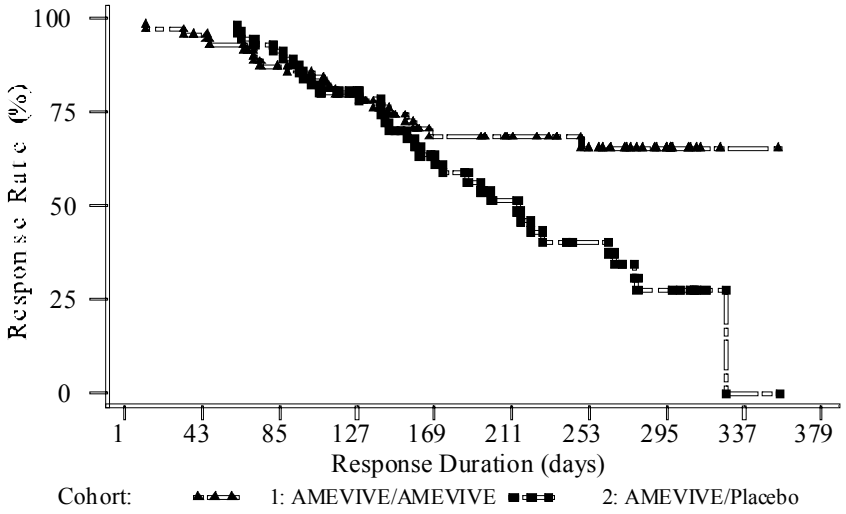


In patients in Study 1 who were randomized to receive two courses of AMEVIVE, 71% achieved a reduction in PASI score of at least 50% from baseline and 40% achieved a reduction in PASI

score of at least 75% from baseline at any time after the start of dosing.
Clinical responses were typically evident within six weeks after the first dose in both studies. Maximal responses were seen during the follow-up interval. Return of disease activity following cessation of treatment was generally slow. A second course of therapy provided additional benefit (*see Action and Clinical Pharmacology, Duration of Effect*).

The Kaplan-Meier curve shown in Figure 3 below illustrates the duration of response over two courses of therapy.

Figure 3: Duration of a 50% reduction from baseline PASI in those who achieved a 75% reduction over both courses of therapy without the use of phototherapy or systemic therapies



Log-Rank test P-value for cohorts 1 vs 2: 0.019

Disease Rebound

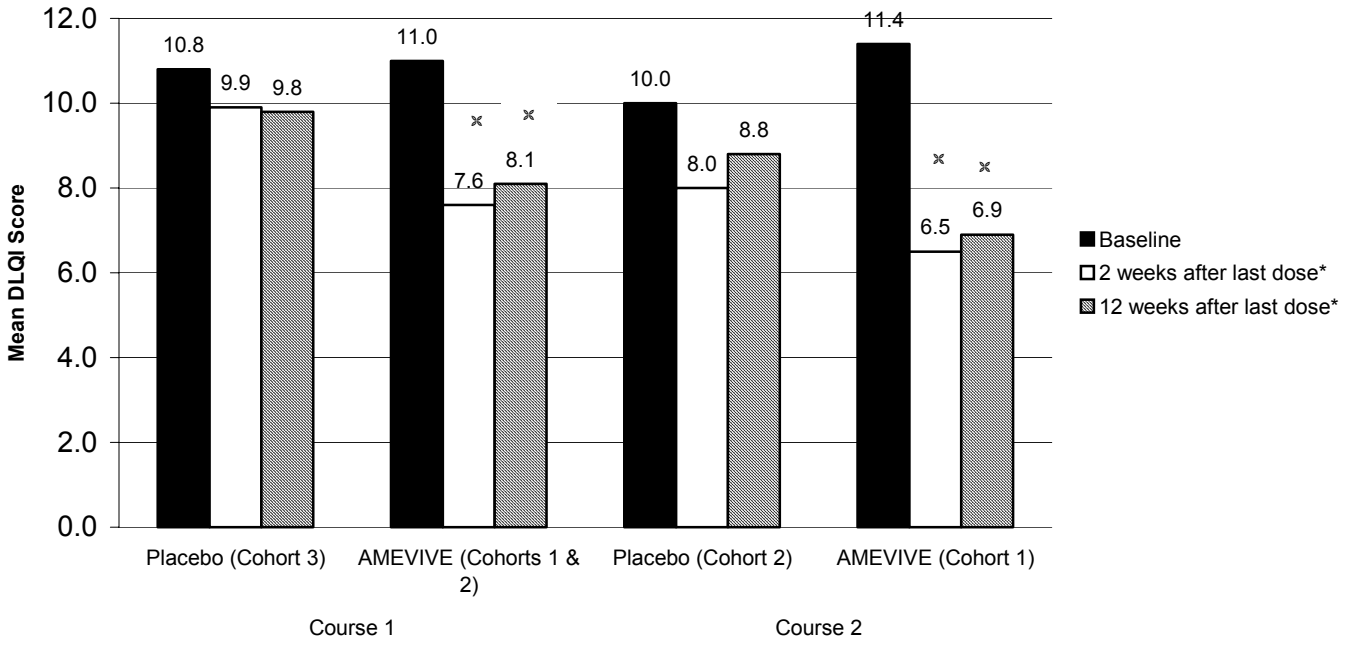
Following cessation of treatment, no disease rebound or flaring occurred at any time in either study.

Quality of Life

Beneficial effects on Quality of Life (QOL), as measured by the Dermatology Life Quality Index (DLQI), were evident in both phase III studies. In Study 1, significant improvements as measured by DLQI were observed in the group treated with AMEVIVE™ (alefacept) compared to placebo as early as two weeks ($p<0.001$) and were sustained for 12 weeks ($p=0.002$) after completion of a course of AMEVIVE (see Figure 4). Patients followed for up to 36 weeks after completion of therapy (Study 1, cohort AMEVIVE/placebo), demonstrated quality of life improvements six months after stopping therapy. Administration of a second course of AMEVIVE was associated with enhancement of the benefit received from the first course. In Study 2, the 15 mg treatment group also demonstrated significant improvements in quality of life

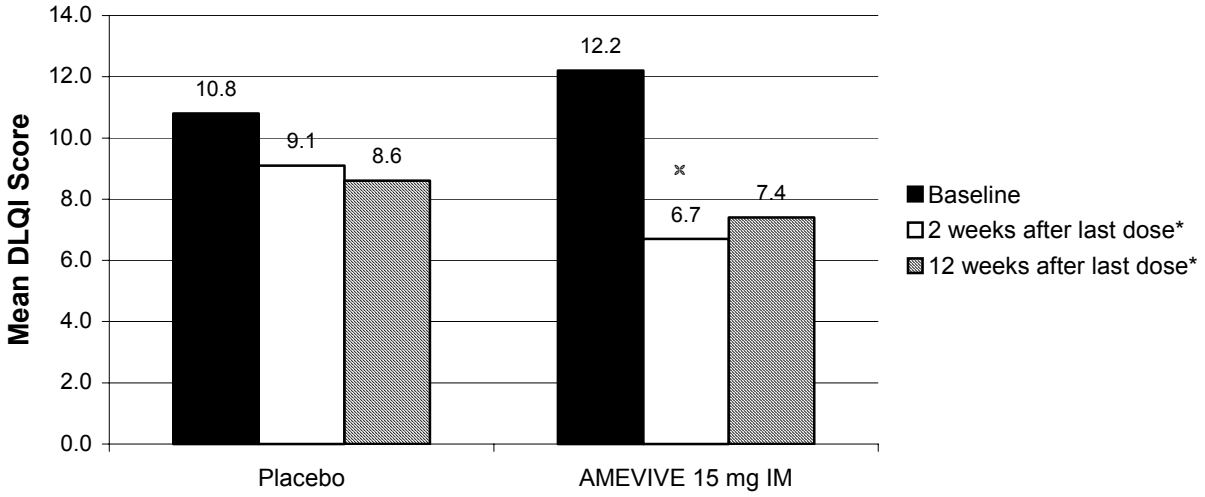
compared to placebo, two weeks after the completion of treatment with AMEVIVE ($p<0.001$) (see Figure 5).

Figure 4: Quality of Life Scores (DLQI) at baseline, 2 weeks and 12 weeks in Study 1



* Adjusted for geographic region, strata, baseline DLQI score, and disallowed concomitant therapy.
⁎ $p \leq 0.026$
Baseline is calculated for patients with at least one post-baseline measurement. Sample sizes for Course 1 placebo and 7.5 mg group are 172 and 332 (baseline & Visit 17) and 158 and 314 (Visit 13) and for Course 2 cohorts 1 and 2 are 149 and 135 (baseline and Visit 17) and 138 and 117 (Visit 13).

Figure 5: Quality of Life Scores (DLQI) at baseline, 2 weeks and 12 weeks post-treatment in Study 2



*Adjusted for geographic region, strata, baseline DLQI score, and disallowed concomitant therapy.
⁎ p<0.001
Baseline is calculated for patients with at least one post-baseline measurement. Sample sizes for the placebo at baseline and Visit 17 are 156 and 150 for Visit 13. Sample sizes for 15 mg group at baseline and Visit 17 are 149 and 141 for Visit 13.

DETAILED PHARMACOLOGY

Human Pharmacokinetics

The pharmacokinetic characteristics of alefacept are those anticipated for an immunoglobulin-based protein. Single-dose pharmacokinetics adequately predict outcomes after repeat dosing. Volume of distribution (Vd), clearance (Cl), and elimination half-life (t½) are independent of dose and are comparable between healthy volunteers and chronic plaque psoriasis patients. In healthy-volunteer studies, single-dose IV administration of alefacept at doses ranging from 0.005 mg/kg to 0.225 mg/kg showed that serum alefacept concentrations were proportional to the dose administered. Mean Cl, t½, and Vd were relatively consistent and independent of absolute dose. In studies of patients with chronic plaque psoriasis, repeat-dose IV administration at doses ranging from 0.005 to 0.15 mg/kg showed that steady-state serum alefacept concentrations were proportional to dose. The overall disposition was more variable than observed following single-dose administration, although no consistent, dose-dependent trends were observed.

When administered as a fixed dose in the phase III studies, the pharmacokinetics of alefacept were consistent with that observed following repeat dosing based on body weight. Following the weekly administration of alefacept 7.5 mg IV for 12 weeks, mean Cl, t½, and Vd were 0.25 mL/h/kg, 267 hours, and 94 mL/kg, respectively. Following the weekly administration of alefacept 15 mg IM for 12 weeks, mean Cl/F, t½, and Vd/F were 0.46 mL/h/kg, 270 hours, and 167 mL/kg, respectively.

The bioavailability of AMEVIVE following IM administration in healthy volunteer studies was approximately 63%.

No differences in pharmacokinetics have been observed as a function of gender or ethnicity. The pharmacokinetics of AMEVIVE in children or elderly patients or in patients with renal or hepatic impairment have not been studied.

Human Pharmacodynamics

The pharmacodynamic effects of a single dose exposure, a single course or multiple courses of alefacept were qualitatively consistent. CD4+ and CD8+ T cells were most subject to reductions with CD8+>CD4+ and CD45RO+>CD45RA+ cells. IV dosing had a greater effect on lymphocytes than the corresponding IM dose. Recovery after chronic exposure was incomplete over the time period of observation, but was closer to each intra-course baseline for multiple course exposure. Pharmacodynamic efficacy analyses revealed that CD4+CD45RO+ and CD8+CD45RO+ T cell reductions correlated with clinical outcome, with greater reductions predicting increased likelihood of achieving PASI 75% reduction. Clinical response was also associated with T cell reductions in the skin, specifically loss of intra-lesional IFNγ+CD3+ T cells.

Nonclinical Overview

Thirty-five pharmacology and toxicology studies were conducted during the development of alefacept. Nonclinical safety studies with alefacept were conducted in nonhuman primates. All pivotal studies were conducted with representative clinical grade material in compliance with FDA, and international regulatory guidelines. To achieve maximal exposure, alefacept was administered intravenously (IV) in the majority of the nonclinical studies.

Nonclinical Pharmacokinetics

The pharmacokinetics profile of alefacept was evaluated in baboons and cynomolgus monkeys. Administration of alefacept demonstrated predictable and consistent serum concentrations following single and repeat administration. Alefacept serum concentrations were proportional to the dose administered and clearance and elimination half-life were approximately 0.41 mL/hr/kg and 150 hours, respectively. No apparent gender differences in the pharmacokinetics of alefacept were observed. Following intramuscular (IM) administration, the elimination half-life was similar to that observed following IV administration. The bioavailability of alefacept following IM administration ranged from 55% to 61%.

TOXICOLOGY

The toxicologic assessment of alefacept was evaluated in 35 individual studies. Male and female baboons and cynomolgus monkeys were administered alefacept following single-and repeat-dose administration at doses in excess of 100 times the clinical dose for up to 13 weeks in duration. Overall, the single-dose administration through 10 mg/kg and weekly repeat-dose administration through 40 mg/kg was well-tolerated and no mortalities or clinical signs of toxicity were

observed during dosing or post-dose recovery periods. No evidence of opportunistic infections, or global immune compromise were observed in these studies. Immune function testing including delayed-type hypersensitivity (DTH) reactivity and quantifying the antigenic response to exogenous protein antigens showed that alefacept had no effects on humoral or cellular immune function. Test article-related changes included a reversible, dose dependent reduction in absolute lymphocyte counts and T lymphocyte subsets including CD2+ T cells, CD3+ T cells, CD4+ T cells, and CD8+ T cells. Histologic evaluations of tissue sets revealed a consistent, reversible, mild/moderate decrease in the number of small lymphocytes in the spleen and lymph nodes. No changes were observed in the thymus. Immunohistochemical analysis of those same tissues revealed that the histologic findings were consistent with a reduction in CD2+, CD4+ and CD8+ T cells in the peri-arteriolar lymphoid sheath (PALS) of the spleen and in the paracortex of the lymph nodes. The observed changes in T cell populations were accompanied by mild/moderate hyperplasia of CD20+ centroblasts within germinal centers (follicular hyperplasia). The morphology of CD20+ centroblast hyperplasia was consistent with modestly exaggerated clonal responses to normal antigenic stimulation. Normal follicular architecture was also preserved. No adverse effects of alefacept administration were noted in reproductive toxicity studies in primates at weekly doses up to 20 mg/kg. No evidence of genotoxicity was observed in mutagenicity studies.

In a 52-week chronic toxicity study, a single case of an acute B cell lymphoma was observed in one animal. At the time of diagnosis at Week 28, this animal had received over 100 times the cumulative dose for a course of alefacept therapy. Plasma cell/plasmacytiod hyperplasia and polymorphic B cell hyperplasia was also identified in animals treated with alefacept in this study. These findings are different from the centroblast hyperplasia observed in the above mentioned studies and are morphologically and biologically very similar to changes that occur in lymphoid tissues of humans diagnosed with post-transplant lymphoproliferative disease (PTLD) subsequent to immunosuppressive therapy. All animals in the study were positive for an endemic primate Epstein-Barr-like herpes virus also known as lymphocryptovirus (LCV). Gammaherpesvirus-mediated lymphoproliferation is well recognized and well characterized proliferation of B lymphocytes that occurs when humans or nonhuman primates are exposed to immunosuppressive agents. Following a 12-month recovery period none of the remaining animals from each treatment group had any microscopic lymphoid abnormalities, indicating that the lymphoproliferative changes seen in the animals in this study were fully reversible.

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PART III: CONSUMER INFORMATION

AMEVIVE®
alefacept

This leaflet is part III of a three-part "Product Monograph" published when AMEVIVE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about AMEVIVE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

- Biologic medication used to treat psoriasis. Biologics are a class of drugs engineered from proteins (in this case, human proteins) produced by living cells.
- This medicine should be used only under the guidance and supervision of a doctor.
- You should not try to give the injection yourself until you have received the proper training from a health care professional.

What it does:
Psoriasis is a skin disease that starts on the inside and appears on the outside as patches of raised red skin often covered by a flaky buildup (plaques). These plaques can be itchy and at times painful. Psoriasis is an immune disorder. The immune system is your body's defense network against disease. In an immune system disorder, this defense system can actually cause harm to the body. Your immune system is made up of billions of cells, including cells known as T cells. In psoriasis, the T cells become overactive and cause skin cells to multiply 7 to 12 times faster than normal, leading to the appearance of plaques on the skin surface.

AMEVIVE works in two ways. First, AMEVIVE helps prevent T cells from becoming overactive. Second, AMEVIVE selectively lowers the number of overactive T cells in your body, without affecting other areas of the immune system. Because AMEVIVE lowers the number of overactive T cells, many patients continue to improve for months after the injections stop. In these cases, patients may experience treatment free periods. After stopping treatment patients do not experience rapid return or worsening of their disease.

When it should not be used:
People who have a known hypersensitivity to any ingredient in the medicine.

What the medicinal ingredient is:
It is called alefacept, which is a combination of proteins that are found naturally in the body. It has been manufactured using a special process.

What the important nonmedicinal ingredients are:
Citric acid monohydrate, glycine, sodium citrate dihydrate, sucrose. No preservatives.
For a full listing of nonmedicinal ingredients see Part 1 of the product monograph.

What dosage forms it comes in:
Dry powder for reconstitution. When it is mixed with the diluent (sterile Water for Injection), the strength is 15 mg/0.5 mL (cc*) solution for intramuscular injection.
Note: mL and cc reflect the same amount of liquid. You will see cc marks on the syringe.* ***DO NOT use the M marks that also appear on the syringe.* *Refer to the section on How to Prepare and Inject a Dose of AMEVIVE for more information.*

WARNINGS AND PRECAUTIONS

Before you start AMEVIVE and every two weeks during your treatment, your doctor will arrange for blood tests to be taken to measure the level of certain T cells in your immune system. Depending on the results of these tests, your doctor will decide whether you need to postpone or stop taking AMEVIVE. Every two weeks before your injection, your health care professional will tell you whether your T cell count is at an acceptable level before you take your injection. You should continue your treatment unless your health care professional tells you otherwise.

BEFORE you use AMEVIVE talk to your doctor or pharmacist if:

- You have any current health conditions or in the past (including cancer or infection)
- You are taking any other medicines or treatments, including any products you buy, such as over-the-counter medicines and herbal or home remedies
- You have taken AMEVIVE before and had an unusual or allergic reaction or if you have had an allergic reaction to any ingredient
- You are pregnant or planning to become pregnant or are breast-feeding your baby

While you are receiving treatment with AMEVIVE, you need to tell your doctor about any infection that you may experience. If you have a severe infection, your doctor will advise you to stop taking AMEVIVE until your infection is gone.

INTERACTIONS WITH THIS MEDICATION

You may continue to use topical medications to treat your psoriasis such as topical steroids (low-potency) and emollients if your doctor has told you it is okay.

PROPER USE OF THIS MEDICATION

This medicine should be used only under the guidance and supervision of a doctor. Now that your doctor has decided to treat your psoriasis with AMEVIVE, the intramuscular injection can be given in your doctor's office or you may choose to learn how to give the injection yourself. If you and your doctor decide to give the injection yourself, you will be given proper training by a health care professional, through the AMEVIVE Care Program™ or your doctor's clinic, on how to prepare the drug for injection and in proper intramuscular injection technique. You should not try to give the injection yourself until you have received the training.

Usual dose:
The usual adult dose is 15 mg given once a week as an injection into the muscle. The standard treatment period is twelve, once-weekly injections followed by at least a twelve-week break from injections – a treatment free period.

Overdose:
If you receive more medicine at one time than you have been prescribed, you should contact your doctor.

Missed Dose:
If you forget to take a dose on the day it is scheduled, you should contact your doctor.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

As with most drugs, you may experience side effects when taking AMEVIVE. The most common side effects seen in clinical studies (experienced by more than 5% of patients) included headache, sore-throat, accidental injury, runny nose, infection, flu-like symptoms, itch, chills, feeling tired, pain, diarrhea, nausea, viral infection, dizziness and sinusitis. You may experience a reaction at the site of your injection. These reactions are generally mild and usually occurred on single occasions and included pain, inflammation, bleeding, swelling, non-specific reaction, lump or skin hypersensitivity.

Overall, the number of side effects experienced by patients in clinical studies was similar to placebo and was also similar in patients who took more than one course of AMEVIVE. This is not a complete list of side effects. Contact your health care professional if you experience any unexpected effects while taking AMEVIVE.

Infections: Because of the way AMEVIVE works, there may be a drop in the levels of certain types of blood cells that help to fight infections. You should inform your doctor as soon as possible if you develop an infection.

It is important to regularly tell your health care professional about how you are feeling and if you have developed any new symptoms while taking AMEVIVE.

HOW TO STORE IT

Check the expiry date on the vial of AMEVIVE and the diluent (Water for Injection). Do not use after the last day of the month stamped on either vial. You should store the dose administration pack in the refrigerator between 2°C to 8°C. If you do not have enough room in your refrigerator for the full administration dose pack, you can store the vial of diluent and the syringe, needles, bandage, alcohol pads, and gauze pads at room temperature.

However, the vial of AMEVIVE must be stored in the refrigerator. If you don't have access to a refrigerator for a short time, you can keep the vial of AMEVIVE at room temperature for up to 48 hours only.

You may want to take one AMEVIVE administration dose pack out of the refrigerator 30 minutes before you plan to inject your dose to allow it to reach room temperature. This is because a room temperature solution is more comfortable to inject. Once you mix the vial containing AMEVIVE with the diluent, you should inject the solution right away. If necessary you can keep the solution in the AMEVIVE vial for up to 4 hours in the refrigerator between 2°C to 8°C. ANY AMEVIVE NOT USED IN 4 HOURS SHOULD BE THROWN AWAY.

See below for instructions on how to prepare the injection.

How to Prepare and Inject a Dose of AMEVIVE® (alefacept)
Find a clean, flat work surface with good lighting and collect all the supplies you will need to give yourself or to receive an injection.
You will need the following supplies:

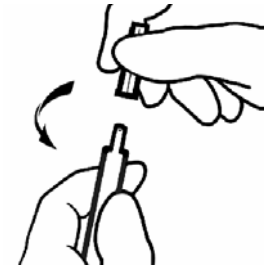
- vial of AMEVIVE
- vial of diluent (Water for Injection, USP)
- syringe
- two sterile needles
- alcohol wipes
- gauze pad
- adhesive bandage
- a puncture resistant container for disposal of used needles

Preparing the solution of AMEVIVE® (alefacept)
It is important to keep your work area, your hands and your injection site clean to minimize the risk of infection. You should wash your hands prior to preparing the medication.

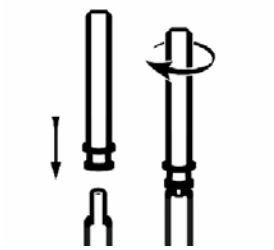
1. Check the expiration date on the vial of AMEVIVE and the vial of diluent. Do not use if the medication or diluent is expired.
2. Remove the coloured caps from the vial of AMEVIVE and the vial of diluent. Do not remove the rubber stoppers or

metal rings. Clean the rubber stopper on the top of each vial with an alcohol wipe. Do not touch the rubber stoppers with your hands after cleaning them.

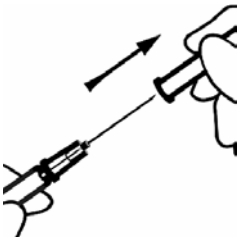
3. Remove the protective cover from the end of the syringe barrel with a counterclockwise turn.



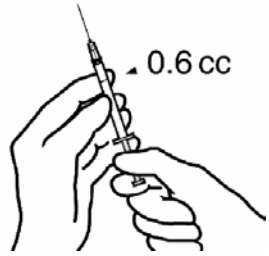
4. Open the wrappers that contain the needles by peeling apart the tabs and set the needles aside. Attach one of the needles to the syringe by pushing it on the syringe.



5. Hold the barrel of the syringe with one hand and pull the needle cover off with the other hand. Do not twist the cover off. Do not touch the needle or let it touch any other surface.

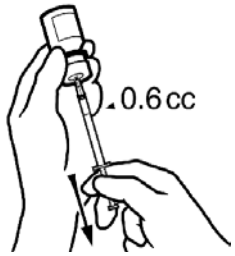


6. Pull back the syringe plunger to the 0.6 cc mark. The syringe has cc marks and not mL marks. Note that cc and mL are the same volume. **DO NOT use the M marks that also appear on the syringe.**

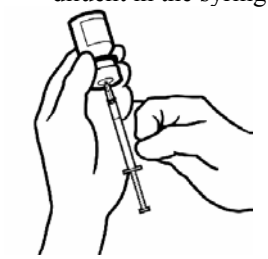


7. With the diluent vial on the flat work surface, firmly push the needle down through the centre of the rubber stopper.

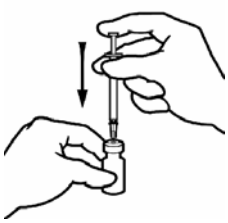
8. Inject the air in the syringe into the diluent vial by pushing down on the plunger until it cannot be pushed any further.
9. Keeping the needle in the vial, turn the diluent vial and syringe upside down.
10. While keeping the needle in the liquid, slowly pull back on the plunger to withdraw 0.6 cc (mL) of the liquid into the syringe.



11. Gently tap the syringe with your finger to make any air bubbles rise to the top. If bubbles are present, slowly press the plunger in (to push just the bubbles out through the needle). If you push diluent back in to the vial, slowly pull back on the plunger and withdraw the correct amount back into the syringe. Make sure there is still 0.6 cc (mL) of diluent in the syringe.



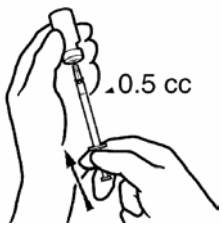
12. Slowly pull the needle out of the diluent vial.
13. Carefully insert the needle through the centre of the rubber stopper of the vial of AMEVIVE. Note: if the needle is not pushed through the centre of the stopper, it may cause the stopper to fall into the vial. If the stopper falls into the vial, do not use.
14. Slowly inject the diluent into the vial of AMEVIVE. DO NOT aim the stream of diluent directly onto the AMEVIVE powder. Too direct or forceful a stream of diluent onto the powder may cause foaming, and make it difficult to withdraw AMEVIVE.



15. Remove the syringe and needle and gently swirl the vial until the AMEVIVE is dissolved. DO NOT SHAKE.

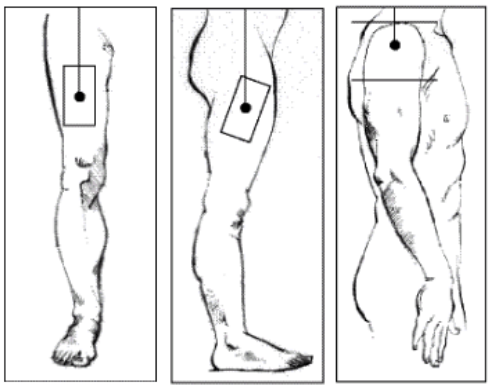
16. Check to see that all of the AMEVIVE powder is dissolved. This usually takes about two minutes. Check the solution in the vial of AMEVIVE to see if it is clear and is a colourless to slightly yellow solution. The vial should not have any particles. Do not use the vial if the solution is cloudy, if it has particles in it or if it is any other colour except slightly yellow.
17. Remove the needle used for reconstitution from the syringe and put the used needle in the puncture resistant container provided. Now attach the second supplied needle to the syringe. Hold the syringe barrel with one hand and pull the needle cover off with the other hand. Do not twist the cover off. Do not touch the needle or let it touch any other surface.
18. Insert the syringe with the new needle into the vial of AMEVIVE and turn the vial and syringe upside down. Slowly pull back on the plunger to withdraw the total volume of AMEVIVE. Some foam or bubbles may remain in the vial.

19. Check the contents of the syringe. It should be a clear and colourless to slightly yellow solution. Do not use the syringe if the appearance is not normal. Get a new set of materials including the syringe and start again from step 1.
20. With the vial still upside down, tap the syringe gently with your finger to make any air bubbles rise to the top. Press the plunger until the AMEVIVE is at the top of the syringe and the plunger reaches the 0.5 cc (mL) mark. Withdraw the needle and syringe from the vial. Do not touch the needle or allow it to touch any surface. Do not touch the syringe plunger as this could cause liquid to leak out.



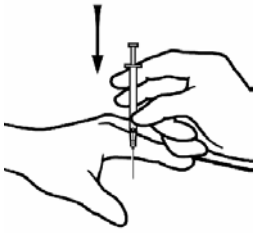
Selecting an injection site

21. The best sites for an intramuscular injection are the thigh and upper arm. You should use different injection sites each week. Make sure that the site you choose doesn't have any skin irritations.

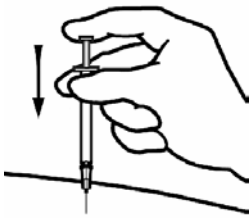


Injecting the AMEVIVE® (alefacept) dose

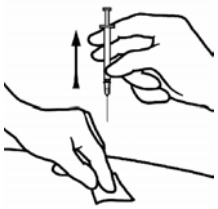
22. Use a new alcohol wipe to clean the skin at one of the recommended intramuscular injection sites.
23. With one hand, stretch the skin out around the injection site. Hold the syringe like a pencil with the other hand, and using a quick motion insert the needle straight down at a 90° angle through the skin and into the muscle.



24. Once the needle is in, let go of the skin and use that hand to gently pull back slightly on the plunger. If you see blood come into the syringe, withdraw the needle from the injection site and put pressure on the site with a gauze pad. You will need to get a new set of materials and start the process again at Step 1.
25. If no blood came into the syringe, slowly push the plunger in until the syringe is empty.

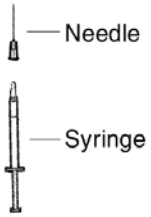


26. Hold a gauze pad near the needle at the injection site and pull the needle straight out. Use the pad to apply pressure to the site for a few seconds or rub gently in a circular motion.



27. If there is bleeding at the site, wipe it off and, if necessary, apply an adhesive bandage.

Disposal of syringes and needles
The used needles should be put into the puncture resistant container. NEVER use a syringe or needle more than once. The diluent vial and the empty vial of AMEVIVE® (alefacept) and syringe should be put into the garbage. DO NOT RECYCLE. DO NOT throw used needles into the household garbage. Keep the puncture resistant container out of the reach of children. DO NOT recycle the container.



REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness
Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

Patients taking AMEVIVE® (alefacept) have access to the AMEVIVE Care Program®. This program provides access to a registered nurse 24 hours per day, 7 days a week. The program offers a variety of product support services and a number of training and administration options, including:

- Self-injection after training by an AMEVIVE Registered Nurse
- Self-injection after training in your physician's clinic
- Nurse administered injections in your physician's clinic
- Nurse administered injections at home or other location

Information about psoriasis and AMEVIVE is available upon request from Astellas Pharma Canada Inc. at 1-877-AMEVIVE (263-8483).

This leaflet was prepared by Astellas Pharma Canada Inc.

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