Food and Drug Administration
Center for Drug Evaluation and Research

SUMMARY MINUTES OF THE

DERMATOLOGIC AND OPHTHALMIC DRUGS ADVISORY COMMITTEE

May 23, 2002

Kennedy Ballroom
Holiday Inn
8777 Georgia Avenue
Silver Spring, Maryland

Members Present
Elizabeth Abel, M.D.
Roselyn Epps, M.D.
Robert Katz, M.D.
Lloyd E. King, Jr., M.D. Ph.D.
Paula Knudson (**Consumer Representative)**
Sharon Raimer, M.D.
Ming Tan, Ph.D.

Consultants to the DODAC
Lynn Drake, M.D., Acting Chair
Warwick Morison, M.D.
Seth Stevens, M.D.
J. Richard Taylor, M.D.

FDA Participants
Jay Siegel, M.D.
Karen Weiss, M.D.
Louis Marzella, M.D., Ph.D.
Ezio Bonvini, M.D.

Executive Secretary (Acting)
Karen M. Templeton-Somers, Ph.D.

Guest Speaker
Robert Swerlick, M.D.

I certify that I attended the May 23, 2002 Dermatologic and Ophthalmic Drugs Advisory Committee meeting and that these minutes accurately reflect what transpired.

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Karen M. Templeton-Somers, Ph.D.
Acting Executive Secretary

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Lynn Drake, M.D.
Acting Chair

At 8:30 a.m. on May 23, 2002, the meeting was called to order by Lynn Drake, M.D., Acting Chair. This was followed by the conflict of interest statement, read by Karen M. Templeton-Somers, Ph.D., Acting Executive Secretary, and the introduction of meeting participants. There were approximately 350 people in attendance.

Call to Order and Opening Remarks	Lynn Drake, M.D. Acting Chair, DODAC
Introduction of Committee	
Conflict of Interest Statement	Karen M. Templeton-Somers, Ph.D. Acting Executive Secretary, DODAC

License # STN BL 125036/0 **Alefacept** **Biogen, Inc.**

Indication: for the treatment of patients with chronic plaque psoriasis who are candidates for phototherapy or systemic therapy

Introduction	Ezio Bonvini, M.D. Division of Monoclonal Antibodies Office of Therapeutics Research & Review Center for Biologics Evaluation and Research FDA
Sponsor Presentation	Biogen, Inc.
Overview:	Burt Adelman, MD Executive Vice President Research and Development
Clinical Experience:	Akshay K. Vaishnaw, MD, PhD Director, Medical Research
Clinical Safety:	Gloria Vigliani, MD Vice President, Medical Research
Alefacept Risk Benefit Profile:	Mark Lebwohl, MD Chairman, Professor of Dermatology Mount Sinai School of Medicine
FDA Presentation	Louis Marzella, M.D., Ph.D. Division of Clinical Trial Design & Analysis OTRR, CBER, FDA

Open Public Hearing

Gail M. Zimmerman - National Psoriasis Foundation
Diane Lewis - National Psoriasis Foundation
Maryellen Crawford - National Psoriasis Foundation
Sean Morton - National Psoriasis Foundation
Alan Menter, M.D. – Psoriasis Specialists Patient Advocacy Group

Questions to the Committee

I. Safety of Alefacept

A. Lymphocyte reduction and risk of infection

Alefacept treatment causes reductions in total lymphocyte counts and T cell subsets. In study 711 (IV study), approximately half of the participants experienced at least a single occurrence of a CD4 cell count below the lower limit of normal at any time during a treatment course (12-week dosing and 12 week follow-up). In study 712 (IM study), this figure was approximately 30%. In some patients, lymphocyte reductions are long lasting. Twelve weeks following the last dose, approximately 20% of study 711 participants had CD4 counts below normal.

The total experience of patients receiving more than 2 cycles is limited. Approximately 50% (N=756) of total alefacept treated patients received 2 courses of treatment, 15% (N=199) received 3 courses, and 10% (N=140) received 4 or more courses. Available data (based on two cycle of treatment) suggest that lymphocyte reductions may be cumulative in some people.

A central issue is whether lymphocyte reductions result in clinical sequelae. In the phase 3 trials, serious infections were reported in 1/413 (0.2%) of placebo and 8/876 (0.9%) of alefacept treated patients. There was no apparent relationship between lymphopenia and infections, and no opportunistic infections were observed. However, some of the infections among patients on alefacept were associated with a protracted course (e.g. cellulitis→septic shock and multi-organ failure, external otitis→facial cellulitis)

The maximum duration of alefacept treatment was 3 months, with a minimum interval of 3 months prior to subsequent dosing. Normal lymphocyte and CD4+ cell counts were required before the first treatment cycle and normal CD4+ cell counts required for subsequent cycles. If licensed, lymphocyte monitoring and dose adjustments may not be as frequent as was performed in the clinical trials. This raises concerns that depth and duration of lymphopenia may be more pronounced, with unknown clinical consequences.

1) Has the sponsor generated sufficient data pre-marketing to characterize treatment related effects on lymphocyte reductions? Given that the sponsor is proposing the product be indicated for multiple cycles, please comment on the adequacy of the data to support multi-cycle use.
2) Please discuss the optimal way(s) to generate additional data on infectious risks.

The Committee has concerns about the treatment-related reductions in lymphocytes, and would like more data on the effects of multiple cycles of alefacept. Non-responders should not be re-treated with alefacept. A patient registry is highly recommended, as well as some more randomized, controlled studies. A registry would be the best way to detect the occurrence of rare events and should be very

inclusive, with careful collection of data on lymphocyte counts, infections, malignancies and surrogate markers (such as C-reactive protein).

B. Changes in antigen response

The effects of alefacept on delayed-type hypersensitivity (DTH) were evaluated in two trials, Study 703 (an uncontrolled dose-escalation study) and 708 (a controlled dose-ranging study). Responses to seven microbial antigens applied to non-lesional skin were evaluated. DTH shifts from + to – were observed for isolated antigens (range 0-3 per patient) in study 703 without relationship to dose. In study 708 the number of DTH shifts from + to – was higher in the alefacept groups compared to placebo. There are no reports of patients treated with alefacept who developed tuberculosis. No studies have been performed to evaluate the ability to mount a response to vaccines.

1) Should all individuals be evaluated for latent tuberculosis infection with a tuberculin skin test prior to therapy with alefacept? If a latent infection is uncovered, please discuss how such individuals should be managed with respect to use of alefacept.

The Committee recommends that alefacept be treated like the other immunosuppressives, with the same standard tests before prescribing.

2) Should subject monitoring include periodic assessments of DTH? No.

3) Should the sponsor perform studies to evaluate the ability to respond to immunizations such as pneumococcal or influenza vaccines?

The Committee advised that the pediatric and geriatric populations are especially at risk for compromised immunizations and this should be studied before marketing the drug for these populations. All reasonable and rational precautions should be taken with these and other high risk populations. Very careful followup and periodic reviews are recommended. A recommendation that the threshold for withholding the next alefacept dose (currently CD4+ count <300) be modified for special populations was endorsed by the Committee.

C. Malignancies

Individuals with severe psoriasis are at higher risk for developing malignancies, particularly skin malignancies (squamous cell carcinoma) and lymphomas. The pathophysiology of the disease and more importantly some of the treatments (PUVA, etc) may predispose to neoplasia. Alefacept is a new biological with known immunosuppressive effects. In the controlled studies, rates of malignancy were: 2/413 (0.5%) for placebo and 10/876 (1.1%) for alefacept treated patients. Most of the malignancies were squamous cell skin cancers though one alefacept treated patient developed B cell lymphoma during an open label extension, and a single occurrence of B cell lymphoma was seen in a non-human primate study.

It is difficult to detect an increase in the rate of malignancies in the absence of larger numbers of patients exposed and longer periods of follow up and in the absence of a concurrent control group.

1) Please discuss how best to evaluate the risk of malignancies. Should all people who receive alefacept enter a registry?

*In general, the recommendations for evaluating the risk of malignancies are the same as discussed for **A. Lymphocyte reduction and risk of infection** and **B. Changes in antigen response,** with the caveat that malignancies are much slower to develop than infections and so require a much longer timeline. Data on B-cell hyperplasia should also be included in the registry portfolio.*

II. Dose

In the phase 2 study, dosing was weight based. Weight did not appear to be an important factor in the pharmacokinetic profile of alefacept. Thus, the phase 3 studies were conducted using fixed doses for both the IV and IM routes of administration, with the exception that very low weight subjects (< 50kg) received a 30% reduction in the dose. In study 711, efficacy responses were approximately 4 fold less in people weighing >85 kg vs ≤85 (5% vs 19%, respectively after adjusting for placebo effect). Similar trends in response were seen in study 712 (IM study), where response rates for people >85 kg and ≤85 kg were 12% vs 19%, respectively after adjusting for placebo effect. This suggests that heavier study subjects may have been under-dosed; however, such patients appeared to experience a degree of lymphopenia similar to those who were below the weight median.

1) Please discuss the degree to which the dose has been optimized. Should the sponsor conduct further studies of weight-based dosing?

The Committee held mixed views on whether dosing should be fixed or weight-adjusted. A fixed dose appears to be fine for intramuscular administration. Adjustments in dosing might be necessary for patients at both weight extremes and for children. A post-market study on shorter dosing courses (less than 12 weeks) was suggested.

III. Efficacy Outcomes

In the phase 3 studies the primary assessment was the proportion of patients with ≥75% improvement in PASI score from baseline. Patients receiving systemic therapy or phototherapy were considered treatment failures in the primary efficacy analysis. Physician's Global Assessment (PGA) of "clear" or "almost clear" was an important secondary outcome. By PASI assessment, 10-16% (absolute) more alefacept-treated patients responded compared to placebo, and 7-9% (absolute) more alefacept-treated patients responded by PGA assessment.

Of three different instruments used to assess patient reported outcomes, the overall Dermatology Life Quality Index (DLQI) score was considered to be the primary score. The DLQI score ranges from 0 (best) to 30 (worst). The DLQI was measured at baseline and after the end of treatment. The between group difference, which favored alefacept, was no more than 3 points after adjusting for baseline DLQI score.

1) Please discuss the choice of ≥75% improvement in PASI to demonstrate clinical benefit with the PGA of clear or almost clear as the key secondary outcome measure.

This question was not directly addressed, but the topic was discussed extensively during the general discussion. PASI-50 may be a more reasonable outcome measure. Details can be found in the transcript.

2) Do the DLQI data suggest a meaningful benefit over and above that provided in the PASI and PGA outcomes?

The Committee felt that all three assessments should be considered – PASI, PGA and DQLI (but did not feel the DLQI data was informative enough to include in detail in a label – see question V.5). As such, alefacept appears at least as effective as other agents. The current safety profile is based on a relatively small population, and it is expected that more safety concerns will arise when a larger segment of this highly vulnerable population undergoes alefacept treatment. Long term monitoring for malignancies is very important.

IV. Risk/Benefit

1) Has the sponsor shown that alefacept is safe and effective for use in adults with chronic plaque psoriasis?

Yes – 8 ***No – 2*** ***Abstain – 1***

2) If the answer is yes, then, please comment on the issues regarding the product label, as discussed below.

V. Product Label

The sponsor has proposed that the indicated population be "patients with chronic plaque psoriasis who are candidates for phototherapy or systemic therapy." Eligibility criteria permitted enrollment of individuals who had received prior systemic or phototherapy as well as those who were naïve to such prior therapies.

1) Should the indicated patient population be limited to people who have failed or had an inadequate response to phototherapy or systemic therapy rather then "candidates for" such therapies?

Open access is recommended, not limiting alefacept use by previous treatment. The Committee advocates special caution for those at high risk for malignancies, including those who have undergone PUVA therapy.

2) Should the indication specify 'moderate to severe' plaque psoriasis?

Yes. The Committee feels that these patients have the most favorable risk:benefit profile.

3) Please discuss the recommendations that should be included in the label regarding lymphocyte monitoring and subsequent dosing. Specifically, should the label state that lymphocyte counts and CD4 counts be followed for all subjects as was performed in the clinical studies?

Yes, the registry recommended earlier should include data on that lymphocyte counts and CD4 counts.

4) Please comment on the types of information to include in the warnings regarding the risks of infection and malignancy.

Patients should be followed closely for infections and malignancies, especially the pediatric and geriatric populations and those with concomitant indications.

5) What, if any, information regarding the DLQI outcomes would be useful to provide in the product label?

Because quality of life measures are easily misinterpreted, the DQLI outcomes should only be mentioned in the label in a generalized way, perhaps with the provision of a reference.

VI. Studies in Other Populations

A. Adults with other forms of psoriasis

Individuals with erythrodermic, guttate, palmar, plantar pustular, or generalized pustular psoriasis were excluded from the clinical studies.

1) Should the sponsor evaluate the safety and efficacy of alefacept in people who have other forms of psoriasis?

   Yes, especially those with erythrodermic and pustular psoriasis.

B. Children

Pediatric patients have not been evaluated in the clinical development program thus far. Federal regulations require sponsors to conduct trials in pediatric populations for a use approved in adults if the product is to be used in large numbers of affected children or it represents a meaningful therapeutic benefit. Trials in children may be deferred to after market approval for adults, particularly if concerns about toxicity warrant the collection of more safety data in adults before children are exposed. Biogen has requested and received a deferral for the conduct of pediatric studies.

1) Should alefacept be studied in pediatric patients with psoriasis? If so, please discuss the timing of such studies relative to accumulation of postmarketing safety data in adults.

2) What are appropriate efficacy outcomes for pediatric studies?

3) How should children be assessed for loss of response to recall antigens or ability to respond to childhood vaccines?

The Committee indicated that controlled trials are needed in the pediatric population, after more safety data is available from the adult population. Children usually respond well to UVB, so it is prudent to get more data from adults before using alefacept extensively in the pediatric population. Children with psoriatic arthritis should be studied, as they are often on systemic medications and have the potential to show more benefit from alefacept.

C. People with concomitant HIV infection

HIV infection was an exclusion criterion. HIV is a precipitating factor in psoriasis.

1) Given the effects on lymphocyte depletion, please discuss whether patients with concomitant HIV infection should be studied. If studies are appropriate, please discuss what lymphocyte values should be considered for dosing decisions. If studies are not warranted, what information should be included in the label about use in persons with HIV (and other populations at risk of infections)?

There are no data on alefacept in this population, because HIV was an exclusion criteria in the trials. This population is already at high risk for opportunistic infections. Patients should be tested for HIV and hepatitis before starting alefacept. Some members thought it would be important to carefully

The meeting adjourned on May 23, 2002 at 4:15 p.m.

Prepared by:

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Acting Executive Secretary
Dermatologic and Ophthalmic Drugs Advisory Committee