

Food and Drug Administration
Center for Drug Evaluation and Research

**SUMMARY MINUTES
ARTHRITIS ADVISORY COMMITTEE**

September 16, 1998
Holiday Inn Gaithersburg
2 Montgomery Village Avenue, Gaithersburg, MD

Members Present

Michelle Petri M.D., M.P.H., Chair
Steven B. Abramson, M.D.
Barbara C. Tilley, Ph.D.
Harvinder S. Luthra, M.D.
Frank Pucino, Jr., Pharm.D.
E. Nigel Harris, M.D.
Matthew H. Liang, M.D., M.P.H.
David E. Yocum, M.D.
Lee Simon, M.D.
Leona M. Malone, MSW

Consultants

Kenneth Brandt, M.D.
David Felson, M.D., M.P.H.
Barbara White, M.D.
Ildy Katona, M.D.
Leigh Callahan, Ph.D.
Marianne Frieri, M.D., Ph.D.
Richard A. Goldsby, Ph.D.
Evelyn Hess, M.D.

Executive Secretary

Kathleen R. Reedy
William Freas, Acting

FDA Participants

Robert DeLap, M.D.
William Schweiterman, M.D.
Kathleen Clouse, Ph.D.
Jeffrey N. Siegel, M.D.
David Green, Ph.D.

Guest Experts

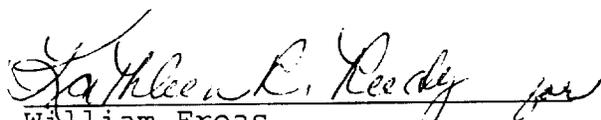
Earl Silverman, M.D.

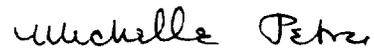
Members Absent

Daniel Lovell, M.D., M.P.H.

These summary minutes for the September 16, 1998 meeting of the Arthritis Advisory Committee were approved on 9/26/99.

I certify that I attended the September 16, 1998 meeting of the Arthritis Advisory Committee and that these minutes accurately reflect what transpired.


William Freas,
Acting Executive Secretary


Michelle A. Petri, M.D., M.P.H.
Chairperson

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The ARTHRITIS ADVISORY COMMITTEE met on September 16, 1998 at the Holiday Inn Gaithersburg, 2 Montgomery Village Avenue, Gaithersburg, MD to consider BLA 98-0286, etanercept (Enbrel™) sponsored by Immunex. The committee had been provided a background document from both the sponsor and the agency approximately 18 days before the meeting. Approximately 250 people attended the meeting.

The meeting was called to order at 8:00 am by Michelle Petri, M.D., M.P.H., Chair of the Arthritis Advisory Committee. After the members, consultants and agency participants introduced themselves, the meeting statement was read by William Freas, Acting Executive Secretary of the Arthritis Advisory Committee. The opening remarks were presented by Kathleen Clouse, Ph.D., Senior Investigator in the Division of Cytokine Biology, Office of Therapeutics Research and Review (OTRR).

The Immunex Presentation consisted of:

Introduction: Kenneth B. Seamon, Ph.D., Senior Vice President, Drug Development

Clinical Experience: Leslie Garrison, M.D., M.P.H., Senior Medical Director

Summary: F. Ann Hayes, M.D., Senior Vice President, Medical Development

The FDA Center for Biologics Evaluation and Research Presentation was as follows:

Clinical Review: Jeffrey N. Siegel, M.D., Medical Officer

Division of Clinical Trial Design and Analysis, OTRR

Pharmacology Toxicology Review: David Green, Ph.D.

Division of Clinical Trial Design and Analysis, OTRR

There were four speakers at the Open Public Hearing and a letter was read into the record.

The speakers were:

Elizabeth Peterson, Chicago, Illinois, patient

Gloria Baswell, Gadsen, Alabama, patient

Margaret Crowley, Huntsville, Alabama, patient

Noreen Walker, National Arthritis Foundation, Maryland Chapter volunteer and patient

A letter from Judy Schiffer, patient, was read.

The Committee discussion was conducted around the following issues and questions. proceeded.

1. The role of Enbrel on the development of infections is unknown. In the largest randomized study, (16.0009), twice as many Enbrel-treated patients treated at the highest dose as placebo-treated patients developed upper respiratory infections, although no Enbrel treated patients in this study developed a serious infection. Of the 1039 patients overall with RA who received Enbrel, 19 had a serious infection; 14/19 developed their infection after ≥ 6 months of dosing with Enbrel. At least two Enbrel-treated patients with documented bacterial infections appeared to have had unusually complicated or prolonged illnesses despite appropriate antibiotic treatment, and one patient who received Enbrel died of staphylococcal sepsis. The absence of data from a randomized control group makes causality assessment difficult. Results from other

Enbrel trials and studies of other anti-TNF agents also suggest the potential for infection-related adverse events.

Please discuss the risk of infection associated with Enbrel use. What information relating to this risk should be included in the package insert if the product is approved? Should the sponsor be encouraged to conduct additional studies pre or, if approved, post-marketing to better characterize the infection-related adverse events? If so, what types of studies should be considered?

2. The role of Enbrel on the development of autoantibodies and autoimmune diseases is unknown. In study 16.0009, the number of subjects developing new anti-nuclear antibodies (ANAs) during the study were: 4 placebo subjects, 4 subjects receiving 10 mg Enbrel, and 9 subjects receiving 25 mg Enbrel. The number of subjects with a new positive anti double-stranded DNA (dsDNA) antibody test was: 3 for placebo, 9 for Enbrel 10 mg, and 9 for Enbrel 25 mg. Although few subjects had patterns of rising titers, and no new autoimmune diseases were observed, the long-term risk of developing autoimmune disease is unknown. Data from studies of other anti-TNF agents also suggest the potential for autoimmunity.

Please discuss the risk of autoimmunity associated with Enbrel use. If approved, what information relating to the risk of new autoimmune disease should be included in the package insert? Should the sponsor be encouraged to conduct additional studies post-marketing to characterize the risk of developing positive autoantibody tests and new autoimmune disease with long-term treatment if Enbrel is approved? If so, please discuss the types of studies that should be considered.

3. Enbrel has been administered alone only to patients who have failed DMARDs and never as primary therapy for early RA. In two controlled studies (16.0004 and 16.0009), significantly more patients on Enbrel achieved a 20% improvement in the ACR index compared with placebo treatment. Enbrel was administered as monotherapy to patients who had failed 1-4 DMARDs and who had ≥ 10 swollen joints or ≥ 12 tender joints. Among the small subset of patients who were RF negative, ACR20 rates were not different between either dose of Enbrel or placebo, although responses were observed among Enbrel-treated patients in this subset. In study 16.0014, 59 patients with poorly controlled symptoms on MTX received Enbrel in combination with MTX; 71% (42/59) achieved an ACR20 compared to 27% (8/30) of subjects on MTX alone. No patients have been studied with Enbrel in combination with other DMARDs.

Adverse events observed more often among Enbrel-treated patients included infections, particularly upper respiratory tract infections, and injection site reactions. As discussed in question 1 and 2 above, the role of Enbrel in the development of serious infections and autoimmune diseases is unknown. There is a theoretical risk that malignancies may arise following Enbrel-induced immunomodulation or immunosuppression, although limited data do not suggest higher rates of malignancy with exposure to Enbrel.

Do the safety and efficacy data support an indication for use of Enbrel:

- a) As "monotherapy" in patients with "active" RA (please define) who have failed DMARDs and have disease severity similar to patients studied?
- b) As "monotherapy" in patients with "active" RA without regard to disease severity or prior DMARD use?
- c) As part of combination therapy with MTX? If yes, should the use of Enbrel in combination with MTX be limited to patients who are "failing" (please define) MTX?
- d) As part of combination therapy with other DMARDs?
- e) Please comment on the responses observed in rheumatoid factor negative patients. Should the sponsor be encouraged to further study this group, such as with other doses or schedules?

4. In addition to the results on ACR 20, the sponsor has provided results from HAQ and its components, which indicated that patients who received Enbrel had improvement in scores for disability, mental health, vitality, etc.

Please comment on data regarding functional ability and quality of life. To what extent have beneficial effects been established on disability, mental health, and vitality?

5. The pharmacokinetic (pK) profile of Enbrel in patients with rheumatoid arthritis has not been fully characterized. Pharmacokinetic data were derived from three sources: a) patients treated with only a single dose; b) patients treated with a loading dose followed by maintenance dosing; c) patients treated at the proposed dose and schedule using sparse sampling techniques. Across all studies, and between patients in each study, the clearance varied widely. It is not known which variables could account for the observed differences in clearance, and whether such differences affect safety and efficacy. The sponsor proposes a fixed dose of 25 mg, as was tested in 16.009 and 16.0014, for chronic therapy. Fixed dose regimens emphasize PK differences, although there was no evidence that the lighter patients experienced differences (either safety or efficacy) compared with heavier patients.

- a) Should the sponsor be encouraged to conduct further studies to explore whether a relationship exists between pharmacokinetic parameters and dose and schedule, including weight-adjusted vs. fixed dose regimens? Between pharmacokinetic parameters and patient/disease related characteristics? If so, which patient/disease characteristics would be most important to examine?
- b) Is the proposed fixed dose appropriate for chronic treatment in this setting?

6. As per the 1994 Pediatric Rule, information on pediatric use should be included in product labeling if safety and efficacy are established in the adult population, provided the course of the disease and the drug's effects in pediatric populations are similar to the adult experience, and/or pediatric use is supported by controlled studies in pediatric patients. The sponsor has recently completed a randomized withdrawal study in pediatric patients with rheumatoid arthritis which enrolled children as young as age 4. The current license application contains information from the first phase of the pediatric study, the open-label, uncontrolled, phase; data from the randomized portion were not available for inclusion in the BLA. If approved for use in adult patients with rheumatoid arthritis, labeling could include the information from the uncontrolled phase (e.g., numbers of patients studied, ages, doses, adverse events, etc.) as well as the tatement "safety and efficacy below the age of 16 have not been established".

a) Does the committee concur with inclusion of this type of information in the current label?

b) If the randomized withdrawal study indicate efficacy in JRA, what additional data (clinical or pre-clinical) should be gathered on use of Enbrel in pediatric populations; e.g., effects of Enbrel on growth and development, antibody response to immunization, host response to immunization with live viral vaccines, experience in children with JRA ages 2-4, etc.?

A verbatim transcript of the meeting is available for more detailed examination of the discussion issues.

The meeting adjourned at approximately 5:00 pm.