DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our STN: BL 103795/5162

SEP 24 2004

Immunex Corporation
Attention: Douglas Hunt
Director, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Dear Mr. Hunt:

Your request to supplement your biologics license application for Etanercept to revise the Clinical Studies, Adverse Reactions, and Indications and Usage sections of the package insert (PI) and the Patient Package Insert (PPI) have been approved.

This fulfills your postmarketing commitments:

- To obtain long-term safety data on the development of cancer and autoimmune diseases for all patients enrolled in protocols 16.0018 (long term follow-up study from prior RA or JRA studies) and 16.0023 (long term follow-up study for patients enrolled in protocol 16.0012) and to submit five year safety and efficacy data by December 2003, as stated in commitment number 2 of the June 6, 2000, approval letter for STN 103795/1004 (formerly Reference Number 99-0884).

- To initiate a study to evaluate the concurrent use of Enbrel and Methotrexate by October 1, 1999, as stated in commitment number 5 of the May 27, 1999, letter for STN 103795/1001 (formerly Reference Number 98-1296).

We acknowledge your written commitment to provide additional information and to conduct postmarketing studies as described in your letter of September 17, 2004.

Postmarketing Studies subject to reporting requirements of 21 CFR 601.70:

1. To complete ongoing Study 0881A1-308-EU/AU entitled "A Double – Blind Study Evaluating the Efficacy and Safety of the Combination of Etanercept and Methotrexate in Comparison to Etanercept Alone, or Methotrexate Alone, in Rheumatoid Arthritis Patients. Two year safety data will be submitted by July 2005. A final study report containing three year safety and clinical efficacy data with revised labeling, if applicable, will be submitted by July 31, 2006.

2. To analyze existing data on patient growth parameters collected from protocol 016.0016 entitled "Safety, Population Pharmacokinetics, and Efficacy of Recombinant Human Tumor Necrosis Factor Receptor (p75) Fc Fusion Protein (TNFR:Fc) in Children with

Rheumatoid Arthritis". A statistical analysis plan for analyzing these data will be submitted by January 31 2005 and a final study report along with revised labeling, if applicable, will be submitted by July 31 2005.

3. To obtain 10-year data on the development of cancer and autoimmune diseases for all patients who are enrolled in protocols 16.0018 (long term follow-up study from prior RA or JRA studies) and 16.0023 (long term follow-up study for patients enrolled in protocol 16.0012). Ten-year safety and efficacy data will be submitted in a license supplement by July 31, 2009.

    a. Patient Accrual By: October, 1998
    b. Study Completion By: December , 2008

Pursuant to 21 CFR 201.57(f)(2), patient labeling must be reprinted at the end of the package insert. We request that the text of information distributed to patients be printed in a minimum of 10 point font.

Please submit all final printed labeling at the time of use and include implementation information on FDA Form 356h. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels). In addition, you may wish to submit draft copies of the proposed introductory advertising and promotional labeling with a cover letter requesting advisory comments to the Division of Drug Marketing, Advertising and Communication (HFD-42), Center for Drug Evaluation and Research, 5600 Fishers Lane/Room 8B45, Rockville, MD 20857. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by an FDA Form 2253.

Please refer to http://www.fda.gov/cder/biologics/default.htm for important information regarding therapeutic biological products, including the addresses for submissions. Effective Oct. 4, 2004, the new address for all submissions to this application is:

CDER Therapeutic Biological Products Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence to support that claim.

This information will be included in your biologics license application file.

Sincerely,

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Marc K. Walton, M.D., Ph.D.
Director
Division of Biological Internal Medicine Products
Office of Drug Evaluation VI
Center for Drug Evaluation and Research

Encl: Package Insert (PI)
Patient Package Insert (PPI)

CONCURRENCE PAGE

Letter Type: LETTER: Approval (AP)
LETTER: Fulfillment of PMC
Summary Text: Clinical Supplmt. Efficacy - New/Expanded Indication

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History: michaloski\letters\103795_5162rev.9.22.04.rev.9.23.04

REVIEW COMPLETION REQUIRED BY: RIS

SS Data Check:
- **Place copy of Approval Ltr. with original signature concurrence page in Archival package behind the "Approval Materials" Tab after LAR (Licensing Action Recommendation).**

RIS Data Check:
- **Verify short summary – Ltr. & Submission screen should match.**
- **Check Letter for PMCs (if PMCs – add "PMCs – Approved With" special characteristic code.)**
- **Check if Major Approval – if so – add code.**
- **Perform Review Completion Process**
- **Milestone: Confirm Approved Status**

cc: HFM-573/M. Andrich
HFM-599/A. deMarco
HFM-576/I. Mahmood
HFM-219/S. Misra
HFM-576/E. Papadopoulos
HFM-578/ J. Siegel
HFM-588/E, Dye
HFM-585/K. Schneider
HFM-585/C. Michaloski
HFM-500/K. Weiss
HFM-500/G. Jones
HFM-110/RIMS/R. Eastep
HFD-400/ODS M. Dempsey
HFD-006/Exec sec P. Guinn
HFD-013/FOI D.Taub
HFD-013/FOI H. Brubaker
HFD-230/OTCOM/CDER WebMaster
HFD-001/B. Duvall-Miller (if PMC commitments)
HFD-42/DDMAC/M. Kiester
HFD-410/ODS/DSRCS/ Karen Young
HFD-950/OCTAP/T. Crescenzi
HFD-960/OCTAP/G. Carmouze

HFD-320/DMPQ/ J. Famulare
HFD-322/IPCB/ E. Rivera-Martinez
HFM-555/DMA/ S. Kozlowski
HFM-555/DMA/ K. Clouse
HFM-570/DTBIMP/ M. Walton
HFM-570 C. Lee (if clinical PMC commitments)
HFD-430/ODS/DDRE (hard copy)
HFD-410/CDER Medwatch Safety Labeling (hard copy)
DRMP BLA file (hard copy)

History: Michaloski\letter\103795_5162; rev9.21.04rev9.23.04

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