



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Silver Spring, MD 20993

sBLA 125057/161

**SUPPLEMENTAL APPROVAL**  
April 8, 2010

Abbott Laboratories  
200 Abbott Park Road  
Dept. PA76, Bldg AP30-1NE  
Abbott Park, IL 60064-6157

Attention: Bryan Peterson, Ph.D.  
Associate Director, Global Pharmaceutical Regulatory Affairs

Dear Dr. Peterson:

Please refer to your supplemental biologics license application dated and received December 23, 2008, submitted under section 351 of the Public Health Service Act for Humira (adalimumab).

We acknowledge receipt of your communications dated July 7, September 3, October 28, November 12 and 17, 2009, and January 22 and February 4, 2010.

Reference is made to our September 4, 2008, letter notifying you that, under Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA), a Risk Evaluation and Mitigation Strategy (REMS) is required to ensure the benefits of Humira (adalimumab) outweigh the risks.

This supplemental biologics license application provides for a REMS for Humira (adalimumab).

**RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS**

Section 505-1 of the FDCA authorizes FDA to require the submission of a REMS if FDA becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

Since Humira (adalimumab) was approved on December 31, 2002, we have become aware of new safety information. We have received reports of cases of unrecognized histoplasmosis and other invasive fungal infections associated with concomitant Tumor Necrosis Factor (TNF) blocker use. Humira (adalimumab) is a member of this drug class. A search of the Adverse Event Reporting System (AERS) database found 240 cases of histoplasmosis associated with TNF blocker use. Of these cases, 85% were in the endemic Ohio and Mississippi River valleys. There were 21 cases which contained enough detail to determine that the cases were unrecognized with significant delays in the initiation of antifungal therapy. Of the unrecognized cases, there were 12 deaths, including 5 cases where the diagnosis was only made by autopsy. FDA has also received reports of cases, including deaths, of coccidioidomycosis and blastomycosis in patients receiving TNF blockers. We have concluded that histoplasmosis and other invasive fungal infections in individuals taking TNF blockers may go unrecognized and

untreated leading to deaths that may have been preventable had appropriate treatment been administered. We consider this information to be “new safety information” as defined in section 505-1(b) of the FDCA.

Your proposed REMS, submitted on February 4, 2010, and appended to this letter, is approved. The REMS consists of a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS.

The REMS assessment should include but is not limited to the following:

- a. An evaluation of patients’ and providers’ understanding (i.e. surveys) of the serious risks of Humira (adalimumab).
- b. Specification of measures that would be taken to increase awareness if surveys of healthcare providers indicate that provider awareness is not adequate.
- c. Periodic summaries of adverse reporting of histoplasmosis and other invasive fungal infections including an analysis of deaths and whether appropriate antifungal therapy was instituted promptly.
- d. Based on the information reported, an assessment of and conclusion of whether the REMS is meeting its goals, and whether modifications to the REMS are needed.

Assessments of an approved REMS must include under section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 601.70 and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in Section 505-1(g)(2)(A) of FDCA.

Prominently identify the submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission:

**BLA 125057 REMS ASSESSMENT**

**NEW SUPPLEMENT FOR BLA 125057  
PROPOSED REMS MODIFICATION  
REMS ASSESSMENT**

**NEW SUPPLEMENT (NEW INDICATION FOR USE)  
FOR BLA 125057  
REMS ASSESSMENT  
PROPOSED REMS MODIFICATION (if included)**

If you do not submit electronically, please send 5 copies of REMS-related submissions.

We request that the revised labeling approved today be available on your website within 10 days of receipt of this letter.

**LETTER TO HEALTH CARE PROFESSIONALS**

If you issue a letter communicating important safety-related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this BLA, to [CDERMedWatchSafetyAlerts@fda.hhs.gov](mailto:CDERMedWatchSafetyAlerts@fda.hhs.gov), and to the following address:

MEDWATCH  
Food and Drug Administration  
5515 Security Lane  
HFD-001, Suite 5100  
Rockville, MD 20852

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for information regarding therapeutic biological products, including the addresses for submissions.

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

If you have any questions, please contact Sharon Turner-Rinehardt, Regulatory Health Project Manager in the Division of Pulmonary, Allergy and Rheumatology Products, at (301) 796-2254.

Sincerely,

*//Larissa Lapteva, M.D., M.H.S.//*

Larissa Lapteva, M.D., M.H.S.  
Deputy Director for Safety  
Division of Anesthesia and Analgesia Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure:   REMS  
                  REMS materials  
                  Package Insert with Medication Guide