DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Mary Ann Huizenga, Regulatory Affairs Manager
Abbott Laboratories
200 Abbott Park Road
Abbott Park, IL 60064-6157
Dept. PA76, Bldg. AP30-1E

December 16, 2008

RE: BLA # 125057
HUMIRA (adalimumab) Injection, Solution for Subcutaneous use
MACMIS ID #17035

Dear Ms. Huizenga:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed an American Academy of Dermatology (AAD) Post Meeting News Ad (64V-97007) for HUMIRA (adalimumab) Injection, Solution for Subcutaneous use (HUMIRA) submitted under cover of Form FDA-2253 by Abbott Laboratories (Abbott). This AAD Post Meeting News Ad broadens the approved indication and minimizes the risks associated with the use of HUMIRA. Therefore, this piece misbrands HUMIRA in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. 352(n) and 321(n), and FDA implementing regulations. 21 CFR 202.1(e)(3)(i), (e)(5), (e)(6)(i) & (e)(7)(viii).

Background

According to the **INDICATIONS AND USAGE** section of the approved product labeling (PI)[1], HUMIRA is indicated for the following:

- **Plaque Psoriasis**
  The treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate. HUMIRA should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician.

- **Rheumatoid Arthritis**
  Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active disease. HUMIRA can be used alone or in combination with methotrexate or other disease-modifying anti-rheumatic drugs (DMARDs).

[1] The Professional Brief Summary (Ref: 03-A087-R14, 08A-64D-V621-4 Master) submitted with this advertisement is dated January 2008, and the PI referred to within this letter is also dated January 2008. The most recent approved PI, however, is dated February 2008.

- **Psoriatic Arthritis**
  Reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function. HUMIRA can be used alone or in combination with DMARDs.

- **Ankylosing Spondylitis**
  Reducing signs and symptoms in patients with active disease.

- **Crohn's Disease**
  Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. Reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.

HUMIRA is associated with serious risks, as described in the boxed warning, the WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS sections of the PI.

The boxed warning states:

WARNING: RISK OF SERIOUS INFECTIONS

Tuberculosis (frequently disseminated or extrapulmonary at clinical presentation), invasive fungal infections, and other opportunistic infections, have been observed in patients receiving HUMIRA. Some of these infections have been fatal. Anti-tuberculosis treatment of patients with latent tuberculosis infection reduces the risk of reactivation in patients receiving treatment with HUMIRA. However, active tuberculosis has developed in patients receiving HUMIRA whose screening for latent tuberculosis infection was negative.

Patients should be evaluated for tuberculosis risk factors and be tested for latent tuberculosis infection prior to initiating HUMIRA and during therapy. Treatment of latent tuberculosis infection should be initiated prior to therapy with HUMIRA. Physicians should monitor patients receiving HUMIRA for signs and symptoms of active tuberculosis, including patients who tested negative for latent tuberculosis infection.

The WARNINGS AND PRECAUTIONS section of the PI includes additional important risk information regarding Serious Infections, Malignancies, Hypersensitivity Reactions, Hepatitis B Virus Reactivation, Neurologic Reactions, Hematological Reactions, Use with Anakinra, Heart Failure, Autoimmunity, Immunizations, and Immunosuppression.

The DOSAGE AND ADMINISTRATION section states (in relevant part):

> HUMIRA is administered by subcutaneous injection.
> ...

> The recommended dose of HUMIRA for adult patients with plaque psoriasis is an initial dose of 80 mg, followed by 40 mg given every other week starting one week after the initial dose. The use of HUMIRA in moderate to severe chronic plaque psoriasis beyond one year has not been evaluated in controlled clinical studies.

The January 18, 2008, approval letter for this indication for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate, states:

> [FDA] determined that Humira poses a serious and significant public health concern relating to increased risk for serious infections. This concern required development of a Medication Guide under 21 CFR 208 in order to prevent serious adverse effects, inform patients of information concerning risks that could affect their decisions to use or continue to use the drug, and/or assure effective use of the drug.

To further assess the risks of HUMIRA in the psoriasis population, Abbott committed to conduct a post-marketing prospective, multi-center registry including 5000 adult psoriasis patients treated with HUMIRA in the United States. This commitment was reiterated in the January 18, 2008, approval letter for this new indication. The registry will characterize and assess the incidence of serious adverse events (including serious infections, tuberculosis, opportunistic infections, malignancies, hypersensitivity reactions, autoimmune reactions, and deaths) as well as other adverse events of interest in the study cohort.

Broadening of Indication/Misleading Communication of the Limits of the Indication

The AAD Post Meeting News Ad is misleading because it suggests that HUMIRA is useful in a broader range of conditions or patients than has been demonstrated by substantial evidence or substantial clinical experience. Specifically, the ad includes a prominent statement that HUMIRA is, "**Now approved for moderate to severe chronic plaque psoriasis**" (emphasis in original). This claim misleadingly suggests that HUMIRA is approved for any patient with moderate to severe chronic plaque psoriasis. However, HUMIRA is indicated for the treatment of adult patients with moderate to severe chronic plaque psoriasis **who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate**. As described in the Background section above, the use of HUMIRA is associated with numerous serious risks, including a Boxed Warning for tuberculosis, invasive fungal infections, and other opportunistic infections (some of which have been fatal), as well as other risks described under the Warnings and Precautions and Adverse Reactions sections of the PI.

Healthcare providers need to carefully weigh the benefits and risks of HUMIRA use for each patient, and consider other systemic therapies, as described within the Indications and Usage section of the PI for plaque psoriasis. Furthermore, because of the serious risks associated with this product, HUMIRA should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician. Due to the drug's risk profile, the use of HUMIRA in plaque psoriasis needs to be very carefully considered, a message not conveyed in the ad.

We note that the ad includes the complete indication for chronic plaque psoriasis within the bottom pink section of the ad, located at the end of the first paragraph of text in this section. However, this complete indication is far removed from the above abbreviated and misleading indication, and is presented at the end of a list of HUMIRA's other indications. Additionally, the presentation of the complete indication is written in white text on a pink background in an extremely small font size, rendering this information nearly illegible, while the broad, misleading statement of the indication and the accompanying graphic of the patient are presented very prominently and can be easily seen by viewers of the advertisement.

Additionally, the picture in the ad does not accurately depict a patient with moderate to severe chronic psoriasis who is a candidate for systemic therapy or phototherapy, and in whom HUMIRA would be used when other systemic therapies are medically less appropriate. Rather, the picture shows a small amount of plaque psoriasis on a limited area of the body with part of the plaque cut off on the left side of the page. The small amount of psoriasis shown in the picture does not accurately represent a patient with moderate to severe chronic plaque psoriasis, since moderate to severe chronic psoriasis often involves significant lesions on multiple body surfaces.

In summary, the overwhelming impression created by these misleading presentations broadens the indication for HUMIRA.

Minimization of Risk Information/Lack of Fair Balance

Promotional materials are misleading if they fail to present information about risks associated with a drug with a prominence and readability reasonably comparable with the presentation of information relating to the effectiveness of the drug. Specifically, the AAD Post Meeting News Ad includes the claim that HUMIRA is "**Now approved for moderate to severe chronic plaque psoriasis**" (emphasis in original) along with the picture of a body with plaque psoriasis. This efficacy presentation uses a very large font size and purple type surrounded by a significant amount of white space. In contrast, risk information is presented at the bottom of the page, in white text on a pink background, in extremely small font size, and in single-spaced paragraph format that makes the information extremely difficult to read. This overall presentation misleadingly minimizes the serious risks associated with HUMIRA because it fails to convey this important risk information with a prominence and readability reasonably comparable to the claims of effectiveness in the ad. The overall effect of this presentation undermines the communication of important risk information, minimizing the risks associated with HUMIRA and misleadingly suggesting that HUMIRA is safer than has been demonstrated.

Conclusion and Requested Action

For the reasons discussed above, your advertisement misbrands HUMIRA in violation of the Act, 21 U.S.C. 352(n) and 321(n), and FDA implementing regulations. 21 CFR 202.1(e)(3)(i), (e)(5), (e)(6)(i) & (e)(7)(viii).

DDMAC requests that Abbott immediately cease the dissemination of violative promotional materials for HUMIRA such as those described above. Please submit a written response to this letter on or before January 2, 2009, stating whether you intend to comply with this

request, listing all promotional materials (with the 2253 submission date) in use for HUMIRA as of the date of this letter, identifying which of these materials contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials.

Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266, facsimile at 301-847-8444. In all future correspondence regarding this matter, please refer to MACMIS# 17035 in addition to the BLA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for HUMIRA comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

Andrew S.T. Haffer, PharmD
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications