DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

February 18, 2005

Kevin W. Sharer
Chairman and Chief Executive Officer
Amgen Inc.
One Amgen Center Drive
Mail Stop 17-1-C
Thousand Oaks, CA 91320-1799

RE: STN: BL 103795
Enbrel® (etanercept)
Review #: 040927043

WARNING LETTER

Dear Mr. Sharer:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a 60-second direct-to-consumer (DTC) television advertisement (TV ad) entitled "Freedom" (MIN Z0439) for Enbrel® (etanercept) submitted by Amgen Inc. (Amgen) under cover of Form FDA 2253. The TV ad overstates the effectiveness of Enbrel, fails to communicate the limitations of the indication, thereby broadening the indication, and it minimizes the risks associated with the drug. Thus, the TV ad misbrands the drug within the meaning of the Federal Food, Drug, and Cosmetic Act (Act) (21 U.S.C. 352(n)) and FDA implementing regulations (21 CFR 202.1(e)(3)(ii) & (e)(6)(i)). These violations are concerning from a public health perspective because they encourage use of Enbrel in circumstances other than those in which the drug has been shown to be safe and effective.

Background

According to the FDA-approved labeling (PI), Enbrel is indicated (among other uses): "for the treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy."

With respect to the plaque psoriasis indication, the Clinical Studies section of the PI states (in part):

> Response to treatment in both studies was assessed after 3 months of therapy and was defined as the proportion of patients who achieved a reduction in score of at least 75% from baseline by the Psoriasis Area and Severity Index (PASI). The PASI is a composite score that takes into consideration both the fraction of body surface area affected and the

> nature and severity of psoriatic changes within the affected regions (induration, erythema, and scaling).
>
> . . .
>
> More patients randomized to ENBREL® than placebo achieved at least a 75% reduction from baseline PASI score (PASI 75) with a dose response relationship across doses of 25 mg once a week, 25 mg twice a week and 50 mg twice a week (Tables 8 and 9). . . .
>
> Among PASI 75 achievers in both studies, the median time to PASI 50 and PASI 75 was approximately 1 and approximately 2 months, respectively, after the start of therapy with either 25 or 50 mg twice a week.

Enbrel is associated with serious risks, as described in the Bolded Warning, Warnings, and Precautions sections of the PI:

> **WARNINGS**
>
> **INFECTIONS**
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> **IN POST-MARKETING REPORTS, SERIOUS INFECTIONS AND SEPSIS, INCLUDING FATALITIES, HAVE BEEN REPORTED WITH THE USE OF ENBREL®. MANY OF THE SERIOUS INFECTIONS HAVE OCCURRED IN PATIENTS ON CONCOMITANT IMMUNOSUPPRESSIVE THERAPY THAT, IN ADDITION TO THEIR UNDERLYING DISEASE, COULD PREDISPOSE THEM TO INFECTIONS. RARE CASES OF TUBERCULOSIS (TB) HAVE BEEN OBSERVED IN PATIENTS TREATED WITH TNF ANTAGONISTS, INCLUDING ENBREL®.**
>
> **. . .**
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> **Neurologic Events**
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> Treatment with ENBREL® and other agents that inhibit TNF have been associated with rare cases of new onset or exacerbation of central nervous system demyelinating disorders, some presenting with mental status changes and some associated with permanent disability. Cases of transverse myelitis, optic neuritis, multiple sclerosis, and new onset or exacerbation of seizure disorders have been observed in association with ENBREL® therapy. The causal relationship to ENBREL® therapy remains unclear. . . .
>
> **Hematologic Events**
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> Rare reports of pancytopenia including aplastic anemia, some with a fatal outcome, have been reported in patients treated with ENBREL®. The causal relationship to ENBREL® therapy remains unclear. Although no high risk group has been identified, caution should be

exercised in patients being treated with ENBREL® who have a previous history of significant hematologic abnormalities. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever, bruising, bleeding, pallor) while on ENBREL®. Discontinuation of ENBREL® therapy should be considered in patients with confirmed significant hematologic abnormalities. . . .

Malignancies

In the controlled portions of clinical trials of all the TNF-blocking agents, more cases of lymphoma have been observed among patients receiving the TNF blocker compared to control patients. During the controlled portions of ENBREL® trials, 3 lymphomas were observed among 4509 ENBREL®-treated patients versus 0 among 2040 control patients (duration of controlled treatment ranged from 3 to 24 months). In the controlled and open-label portions of clinical trials of ENBREL®, 9 lymphomas were observed in 5723 patients over approximately 11201 patient-years of therapy. This is 3-fold higher than that expected in the general population. While patients with rheumatoid arthritis or psoriasis, particularly those with highly active disease, may be at a higher risk (up to several fold) for the development of lymphoma, the potential role of TNF-blocking therapy in the development of malignancies is not known (see **ADVERSE REACTIONS: Malignancies**). [endnotes omitted]

PRECAUTIONS

. . .

Patients With Heart Failure

Two large clinical trials evaluating the use of ENBREL® in the treatment of heart failure were terminated early due to lack of efficacy. Results of one study suggested higher mortality in patients treated with ENBREL® compared to placebo. Results of the second study did not corroborate these observations. . . . There have been post-marketing reports of worsening of congestive heart failure (CHF), with and without identifiable precipitating factors, in patients taking ENBREL®. There have also been rare reports of new onset CHF, including CHF in patients without known pre-existing cardiovascular disease. . . .

Immunosuppression

Anti-TNF therapies, including ENBREL®, affect host defenses against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses. . . . The impact of treatment with ENBREL® on the development and course of malignancies, as well as active and/or chronic infections, is not fully understood (see **WARNINGS: Malignancies, ADVERSE REACTIONS: Infections,**

and **Malignancies**). The safety and efficacy of ENBREL® in patients with immunosuppression or chronic infections have not been evaluated.

In addition to the serious risks discussed above, the most common adverse reactions with Enbrel were injection site reactions, upper respiratory infections, and headaches (as identified in the PI section entitled "What are the other more common side effects with Enbrel?").

Overstatement of Efficacy

The TV ad portrays 12 "patients" who have no visible signs of plaque psoriasis. Throughout the vignettes, the images of these individuals' skin (including arms, legs, and sometimes chests or backs that are visible to the camera) reveal no observable sign of any raised, thick, red and scaly patches of psoriasis. The overwhelming impression conveyed by the TV ad is that Enbrel completely clears skin with psoriasis.

Other parts of the TV ad reinforce this message. The audio portion states, "It's a breakthrough that can help." This statement also appears as a headline/graphic SUPER in frame 6 "BREAKTHROUGH." The audio portion states, further, "It can dramatically clear skin fast and help keep it clear month after month." This statement is accompanied by the headline/graphic SUPER "MONTH after MONTH" and the subtitle SUPER "Improvement lasted through 9 months for a majority that saw results," in frame 9. The TV ad also contains the tagline, "Ask your dermatologist about Enbrel and tell psoriasis where to get off--Enbrel" (with accompanying headline/graphic SUPER in frames 15-18).

To our knowledge, Enbrel has not been shown to provide complete clearing of psoriatic skin. As noted above, in clinical trials of Enbrel in plaque psoriasis, more patients in the group receiving Enbrel experienced at least a 75 percent reduction from baseline PASI score, reflecting reductions in the fraction of body surface area affected by psoriasis and improvements in the nature and severity of the disease. We are not aware of substantial evidence or substantial clinical experience demonstrating that Enbrel can provide complete clearing. If you have data demonstrating this benefit, please submit them to FDA for review.

At various times in the ad, small subtitled SUPERs are presented ("Your results may vary," "Not everyone will respond"), apparently in an attempt to qualify the powerful visual/audio/graphic efficacy claims. These SUPERs are not sufficient to disclaim the claim of complete clearing described above.

- Misleading Onset Claim

The claim that Enbrel can dramatically clear skin "fast" also is misleading because consumers are not likely to interpret this claim as meaning that clinical response occurs after two months of treatment as was demonstrated in clinical trials.

- Unsubstantiated Claim

The claim "Enbrel is a breakthrough" is misleading because it is an unsubstantiated claim. Enbrel is not a breakthrough therapy for moderate to severe plaque psoriasis because it does not offer any documented material difference that offers a significant advantage over other drugs already available

for this condition. We are not aware of any head-to-head comparative studies comparing Enbrel to other anti-psoriatic therapies and demonstrating superior effectiveness or safety.

Misleading Communication of the Limits of the Indication

The TV ad is misleading because it fails to clearly communicate to consumers the risk-related limitations to the approved indication. Consequently, the ad suggests Enbrel is useful in a broader range of conditions or patients than has been demonstrated by substantial evidence or substantial clinical experience. Many psoriasis patients with milder disease can be managed adequately with topical therapies that do not have any of the serious risks of Enbrel. Based on the balance of risk to product benefit, only patients with more severe disease (i.e., moderate to severe psoriasis) warrant treatment with Enbrel, because it carries a risk of serious toxicity.

This important limitation to the indication is not prominently communicated in the TV ad. Indeed, this limitation is undermined by use of the unqualified term "PSORIASIS" in the audio and video throughout the ad. For example, the TV ad opens with the announcer voice-over asking the rhetorical questions: "Want to get psoriasis off your back? And chest? And elbows and legs?" Simultaneously, the video presents prominent moving SUPERs repeating these questions ("Want to get PSORIASIS -- Off your BACK? -- And CHEST -- & ELBOWS & LEGS?") as people behind the SUPERs are running, while partially disrobing and displaying their completely clear skin. The Enbrel product name is then introduced with the announcer voice-over claiming: "Enbrel. It's a breakthrough that can help." The simultaneous vignette shows a woman performing a cartwheel while the SUPER overlay states "BREAKTHROUGH." Together with these powerful visuals, the announcer voice-over states: "Enbrel is a different way of treating moderate to severe psoriasis." The next vignette shows a male co-worker wheeling and spinning an exuberant female co-worker around in a roller chair down an office hallway, with the "Enbrel" brand name superimposed over this activity, while at the bottom of the screen is a small subtitled SUPER "For adults with chronic moderate to severe plaque psoriasis." Faced with this visual, graphic, and auditory barrage, consumers are not likely to attend to and process this stated limitation to the indication. The closing frames reinforce the unqualified message that Enbrel is for any severity of psoriasis both in the audio and video graphics. In frames, 15-17, the announcer states "Ask your dermatologist about Enbrel. And tell psoriasis where to get off." The accompanying SUPER presents "and tell PSORIASIS TO GET OFF!" The attempt at disclosing the limitation to the indication in frame 7 does not mitigate the overall misleading message conveyed by the otherwise general characterizations of Enbrel for "psoriasis" which would include patients who are not candidates for systemic or phototherapy. Consequently, by broadening the indication in this way, the ad trivializes the serious risks associated with use of this drug.

Minimization of Risk

The audio communication of serious risk disclosures in the "major statement" is minimized by the distracting visuals and graphics/SUPERs which combine to interfere with the presentation of the risk information. The fast-paced visuals depict a man running down a beach rolling an inner tube and subsequently surfing in the ocean, while the audio component describes the major risks associated with Enbrel. Concurrently, sequential SUPERs are presented describing the potential length of efficacy expected by patients who responded in clinical trials, the product's dosage form, a toll-free number, a reminder to talk to a dermatologist, and a reference to a print ad. The overall effect of the distracting

visuals and graphics, including competing messages related to efficacy, and the competing audio message is to undermine the communication of important risk information, minimizing these risks and misleadingly suggesting that Enbrel is safer than has been demonstrated by substantial evidence or substantial clinical experience. This is particularly troubling as the risks in question are serious, even life-threatening. The viewer should be made fully aware of this.

Conclusion and Requested Action

For the reasons discussed above, the ad overstates the demonstrated effectiveness of Enbrel, inadequately communicates the limitations of the indication and minimizes the serious risks associated with Enbrel therapy. Accordingly, the TV ad misbrands Enbrel under 21 U.S.C. 352 (n) and FDA implementing regulations 21 C.F.R. 202.1(e)(3)(ii) & (e)(6)(i).

DDMAC requests that Amgen immediately cease the dissemination of promotional materials for Enbrel that contain claims the same as or similar to those described above. Please submit a written response to this letter on or before March 7, 2005, describing your intent to comply with this request, listing all promotional materials for Enbrel that contain claims the same as or similar to those described above, and explaining your plan for discontinuing use of such materials. Because the violations described above are serious, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials. Please direct your response to me at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications HFD-42, Rm. 8B-45, 5600 Fishers Lane, Rockville, Maryland 20857, facsimile at 301-594-6771. In all future correspondence on this matter, please refer to Review # 040927043 well as the STN 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 Enbrel comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

Thomas W. Abrams, RPh, MBA
Director
Division of Drug Marketing,
Advertising, and Communications