DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

JUN 18 2003

TRANSMITTED BY FACSIMILE

King & Spaulding
Attention: Eugene Pfeifer
U.S. Agent for: Genpharm Inc.
1730 Pennsylvania Avenue, NW
Washington, DC 20006-4706

RE: ANDA# 75-945
Amnesteem (isotretinoin) Capsules
MACMIS ID# 11661

Dear Mr. Pfeifer:

This letter notifies Genpharm Inc. (Genpharm), and, by copy, Mylan Pharmaceuticals Inc. and Bertek Pharmaceuticals Inc., business operating units of Mylan Laboratories Inc. (Mylan), which markets Amnesteem on behalf of Genpharm, that the Division of Drug Marketing, Advertising, and Communications (DDMAC) of the Food and Drug Administration (FDA) has identified a website for Amnesteem (isotretinoin) Capsules located at www.Amnesteem.com (Website) that suggests that Amnesteem may be effective in alleviating or preventing self-esteem problems and more serious enduring emotional problems in patients with acne. You have also failed to submit your promotional website for Amnesteem to FDA at the time of its initial use. Therefore, your promotion is in violation of the Federal Food, Drug, and Cosmetic Act and its implementing regulations.

Background

Amnesteem was approved on November 8, 2002, for the treatment of severe recalcitrant nodular acne. The prescribing information (PI) for Amnesteem states (emphasis in original) that "[b]ecause of significant adverse effects associated with its use, Amnesteem should be reserved for patients with severe nodular acne who are unresponsive to conventional therapy, including systemic antibiotics." The PI includes a boxed warning that Amnesteem is contraindicated in females of childbearing potential because of a high risk of fetal deformities. The PI also contains a bolded warning on "Psychiatric Disorders" that states as follows:

> "Isotretinoin may cause depression, psychosis and rarely, suicidal ideation, suicide attempts and suicide, and aggressive and/or violent behavior."

Similarly, the Medication Guide for Amnesteem warns patients that "Mental problems and suicide" are possible serious side effects of taking Amnesteem (with signs including recognized symptoms of depression such as sadness, anxiety, empty mood, and feelings of worthlessness).

On February 20, 2003, DDMAC sent a letter notifying Mylan Pharmaceuticals and Genpharm as follows:

> "[Amnesteem] is not approved to modify or prevent illnesses such as depression or to cause an improvement in a patient's psychosocial and emotional well-being. Accordingly, we ask you to pay particular attention in developing your promotional materials to guard against any suggestion that Amnesteem therapy might have such an effect."

The letter further reminded Mylan Pharmaceuticals Inc. and Genpharm of the obligation under 21 C.F.R. § 314.81 to submit copies of all promotional materials to the FDA at the time of initial dissemination (i.e., first use).

The Website, sponsored by Bertek Pharmaceuticals Inc., includes a section directed at patients that prominently displays the Amnesteem logo at the top of the page and continues as follows (emphasis added in italics):

> **More than skin deep**
>
> It's also important to remember that acne can affect more than just the way you look now. If not treated right, it can cause permanent physical scarring. *And because of the way it can affect your self-esteem, acne can cause emotional scars.* For both of these reasons, *if your acne is the source of an unusual amount of worry or stress, you might want to see a* ***dermatologist***.

Unsubstantiated Efficacy Claims and Minimization of Risk

The statements "because of the way it can affect your self-esteem, acne can cause emotional scars" and "if your acne is the source of an unusual amount of worry or stress, you might want to see a **dermatologist**," combined with the prominent logo for Amnesteem heading the page and the title "More than skin deep," suggest that treatment with Amnesteem will alleviate or prevent the self-esteem problems and the resulting "emotional scars" (i.e., more serious, enduring emotional problems) associated with acne, as well as the related worry and stress caused by having acne. Amnesteem is not approved to treat such psychosocial problems, and FDA is not aware of substantial evidence or substantial clinical experience to support these claims. Moreover, this promotion is contrary to the clear direction in our February 20th letter.

We are also concerned that your presentation minimizes the risk, noted in the bolded warning in the Amnesteem PI, that Amnesteem may cause serious psychiatric disorders such as depression, psychosis or suicide. The "More than skin deep" section of your Website omits this important risk information, along with suggesting, to the contrary, that Amnesteem may help alleviate or prevent psychosocial problems, as discussed above.

Failure to Submit Post-Marketing Reports

The Website was not submitted on Form FDA 2253 at the time of initial dissemination, as required by the post-marketing reporting requirements (21 CFR 314.81(b)(3)(i)). This omission is especially concerning because DDMAC reminded Genpharm of this requirement in its February 20th correspondence noted above.

Conclusions and Requested Actions

Genpharm and its agent Mylan (including all of its business units, subsidiaries and affiliates marketing Amnesteem) should immediately discontinue the same or similar violative presentations suggesting Amnesteem for the treatment of psychosocial disorders on its website, as well as any other promotional materials and activities for Amnesteem that contain the same or similar claims. Genpharm should submit a written response to DDMAC on or before July 1, 2003, describing its intent and plans to comply with the above. In its letter to DDMAC, Genpharm should include the date on which these and other similarly violative materials were discontinued.

Genpharm should direct its response to the undersigned by facsimile at (301) 594-6771, or in writing at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications HFD-42, Rm. 8B-45, 5600 Fishers Lane, Rockville, Maryland 20857. In all future correspondence on this matter, please refer to MACMIS ID# 11661 as well as the ANDA number. DDMAC reminds you that only written communications are considered official.

Sincerely,

Sonny Saini, PharmD
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

cc. Mylan Pharmaceuticals Inc.
Attention: Frank R. Sisto

Bertek Pharmaceuticals Inc.
Attention: Sherron P. Wiechert

More than skin deep

It's also important to remember that acne can affect more than just the way you look now. If not treated right, it can cause permanent physical scarring. And because of the way it can affect your self-esteem, acne can cause emotional scars. For both of these reasons, if your acne is the source of an unusual amount of worry or stress, you might want to see a dermatologist.