DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

October 27, 1999

TRANSMITTED VIA FACSIMILE

Charles Heimbold, Jr.
Chairman, CEO
Bristol-Myers Squibb Company
345 Park Avenue
New York, New York 10154

Re: NDA 16-295
Hydrea (hydroxyurea capsules, USP)
Droxia (hydroxyurea capsules, USP)
MACMIS # 8409

WARNING LETTER

Dear Mr. Heimbold:

This Warning Letter concerns a presentation sponsored by Bristol-Myers Squibb Company ("BMS") on September 28, 1999, at the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy ("ICAAC") held in San Francisco, California. The presentation was entitled, "Hydroxyurea and its Role in Treating HIV Disease." The Division of Drug Marketing, Advertising, and Communications ("DDMAC") has concluded that the presentation promoted Hydrea and Droxia for an unapproved use, failed to disclose important safety information, and otherwise misbrands Hydrea and Droxia in violation of the Federal Food, Drug, and Cosmetic Act. See 21 U.S.C. §§331 (a), (b), (d), 352(a), (n), and applicable regulations.

Background

Hydrea and Droxia are branded hydroxyurea products marketed by BMS. The "Indications and Usage" section of the approved product labeling for Hydrea states:

> Significant tumor response to Hydrea (Hydroxyurea Capsules USP) has been demonstrated in melanoma, resistant chronic myelocytic leukemia, and recurrent metastatic or inoperable carcinoma of the ovary.

> Hydroxyurea used concomitantly with irradiation therapy is intended for use in the local control of primary squamous cell (epidermoid) carcinomas of the head and neck, excluding the lip.

The "Indications and Usage" section of the approved product labeling for Droxia states:

> Droxia (hydroxyurea capsules, USP) is indicated to reduce the frequency of painful crises and to reduce the need for blood transfusions in adult patients with sickle cell anemia with recurrent moderate to severe painful crises (generally at least 3 during the preceding 12 months).

The use of Hydrea or Droxia in the treatment of HIV disease is an unapproved use. BMS has not demonstrated, by substantial evidence, that these hydroxyurea products are safe and effective in the treatment of HIV disease.

Promotion of Unapproved Use

Promotional statements or materials are false, lacking in fair balance, or otherwise misleading when they contain representations or suggestions that a drug is useful in a broader range of patients or conditions than has been demonstrated by substantial evidence.

On or before September 26, 1999, BMS or its representatives distributed by mail, or otherwise, materials that announced and invited the recipients to BMS sponsored presentations on HIV research and treatment. The presentations took place at ICAAC on September 26-28, 1999, in the BMS promotional booth in the commercial exhibit hall.

On September 28, 1999, BMS sponsored a presentation entitled, "Hydroxyurea and its Role in Treating HIV Disease." The speaker ("BMS representative") gave a slide presentation that described hydroxyurea as a safe and effective therapy for the treatment of HIV. The slide presentation included a list of several drugs that are indicated for the treatment of HIV disease. Also included in the list were BMS' Hydrea and Droxia. These marketed products are approved for a variety of indications, but not for the treatment of HIV disease. In the presentation, the BMS representative displayed a slide that stated the "activity" of hydroxyurea has been "proven as first line therapy . . . in asymptomatic HIV patients in combination with ddI ± d4T." Furthermore, a slide labeled "Immune Control of HIV," stated "A new triple combination?" followed by the answers: "1. Hydroxyurea 2. ddI 3. Anti-HIV immune response." This presentation suggests that hydroxyurea, in combination with ddI, effectively controls the immune response that occurs with HIV.

Your presentation promoted hydroxyurea as a safe and effective treatment for HIV disease. However, the safety and effectiveness of hydroxyurea in the

treatment of HIV disease has not been established with adequate and well-controlled trials, and this use has not been approved. Therefore, your promotion of hydroxyurea for the treatment of HIV disease misbrands Hydrea and Droxia.

Fatalities With Unapproved Use Not Disclosed

Promotional statements or materials are false, lacking in fair balance, or otherwise misleading if they represent or suggest that a drug is safer, has fewer, or less incidence of, or less serious side effects than demonstrated.

Study ACTG 5025 was a trial funded by the National Institutes of Health ("NIH"). BMS provided study drugs, including the 600mg twice daily dose of hydroxyurea for patients in one arm of the study. The study was designed to determine whether switching patients with documented viral suppression from one treatment regimen to another, with or without the addition of hydroxyurea, prolongs viral suppression. The primary endpoint of the study was loss of viral suppression and drug toxicity necessitating discontinuation of randomized antiretroviral treatment. On or about September 24, 1999, NIH terminated study ACTG 5025 because the rate of discontinuation for drug toxicity was significantly higher in patients randomized to the hydroxyurea treatment arm. Moreover, the hydroxyurea treatment arm had two fatal cases of pancreatitis.

It is our understanding that BMS was made aware of these events on or before September 24, 1999, but in the presentation on September 28th, the BMS representative discussed the use of hydroxyurea in HIV disease and promoted hydroxyurea as "very well tolerated." Furthermore, he presented information about the use of a total daily dose of 1200mg of hydroxyurea in the treatment of HIV disease.[1] Although one slide used by the BMS representative stated that "increasing the daily dose of [hydroxyurea] from 1,000 to 1,500 mg significantly increased toxicity . . .,"[2] the representative failed to disclose that in NIH study ACTG 5025 there was a finding of greater toxicity and two fatal cases of pancreatitis in patients receiving 1200mg/day of hydroxyurea. Thus, although BMS was aware of reports of serious adverse effects and fatalities associated with the use of Hydrea or Droxia in the treatment of HIV disease, and knew that this information was not yet widely publicized in the medical literature, it did not disclose this information.

Conclusion

BMS promoted its hydroxyurea products, Hydrea and Droxia, for the treatment of HIV disease, an unapproved use. Furthermore, BMS failed to disclose certain information related to toxicities and fatalities that were associated with this use of

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[1] RIGHT 702 study – 75 patients received 1200mg of hydroxyurea daily.
[2] ACTG 307 study

hydroxyurea. Thus, BMS stated or suggested that Hydrea and Droxia are safer than has been demonstrated.

Corrective Action Requested

BMS disseminated promotional materials and messages that promoted Hydrea and Droxia for an unapproved use. You also disseminated promotional materials that were misleading and that failed to adequately warn of the risks reported with such use. Accordingly, you should propose an action plan to correct the misleading message disseminated as a result of these violations. As part of this plan, you should:

1) Immediately cease the dissemination of the promotional materials and other promotional messages that contain the same or similar violations.

2) Submit in writing your intent to comply with "1" above.

3) Submit a proposed "Dear Healthcare Provider Letter" that will correct the misleading information you disseminated.

The "Dear Healthcare Professional" letter and your action plan should be submitted to DDMAC for review. After agreement is reached on the content of the letter, you should disseminate the letter by direct mail to all attendees of ICAAC. In addition, you should send the letter to all other healthcare providers who may have received information about the use of hydroxyurea in the treatment of HIV disease from BMS or someone acting on behalf of BMS.

The violations discussed in this letter are not intended to be a complete listing. We are evaluating other aspects of your promotional campaign for your hydroxyurea products and additional violations may be identified. Consequently, we may determine that additional remedial measures may be necessary at a later date to fully correct the false impressions resulting from your improper conduct.

Please respond in writing by November 12, 1999. If you have any questions or comments, please contact Sherrie Shade, R.Ph., J.D. or Tracy Acker, Pharm. D. by facsimile at (301) 594-6771, or by mail at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-42, Rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857.

In all future correspondence regarding this matter, please refer to MACMIS # 8409, and to the NDA number. Only written communications are considered official.

Sincerely,

/S/

Norman A. Drezin, R.Ph., J.D.
Acting Director
Division of Drug Marketing,
Advertising, and Communications