DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MAR -9 1998

TRANSMITTED VIA FACSIMILE

Stephen J. Lenart, RAC
Associate Director, Promotional Compliance
Bristol-Myers Squibb Company
P.O. Box 4500
Princeton, NJ 08543-4500

RE: NDA# 20-357
Glucophage (meformin hydrochloride tablets)
MACMIS ID #6401

Dear Mr. Lenart:

Reference is made to Bristol-Myers Squibb Company's (BMS) December 1, 1997, Form FDA 2253 submission to the Division of Drug Marketing, Advertising and Communications (DDMAC) for Glucophage (metformin hydrochloride tablets). This submission consists of a "Dear Doctor" letter that contains the headline "U.S. Experience Supports the Safety Profile of Glucophage." DDMAC has reviewed this letter and has determined that it is in violation of the Federal Food, Drug, and Cosmetic Act and the applicable regulations. DDMAC finds the letter violative for the following reasons.

The recent revisions to the approved product labeling (PI) for Glucophage were added to address serious potential risk factors for the development of lactic acidosis. These revisions include the addition of the following statements to the PI:

- "Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure (CHF) who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis" added to the CONTRAINDICATIONS and Black Box Warning sections.

- "...treatment of the elderly should be accompanied by careful monitoring of renal function. Glucophage treatment should not be initiated in patients >80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis" added to Black Box Warnings and PRECAUTIONS sections.

- In addition, sepsis has been added to the Black Box Warning section as a condition when Glucophage should promptly be withheld due to increased risk of lactic acidosis

The "Dear Doctor" letter is misleading because it lacks balance and minimizes the significance of these labeling changes by suggesting that BMS voluntarily revised the PI as a courtesy to prescribing physicians in order to facilitate improved appropriate patient selection (e.g. "Read on to find out how we've revised the Glucophage package insert to further improve your ability to appropriately select patients..." and "These revisions are intended to help you better define appropriate patients for Glucophage therapy"). Furthermore, the letter is misleading because it fails to disclose that sepsis has been added to the Boxed Warning section as a condition when Glucophage should promptly be withheld due to increased risk of lactic acidosis.

The statement on page 2 of the letter "Since any of these conditions may increase the risk of lactic acidosis, it is prudent to contraindicate the use of Glucophage in all patients with CHF who require pharmacologic treatment" is misleading because it minimizes the presentation of the boxed warning information and is inconsistent with the PI. The boxed warning states that patients with CHF requiring pharmacologic treatment *are* at increased risk of lactic acidosis (emphasis added).

The claim "Glucophage lowers blood glucose levels by decreasing insulin resistance..." is misleading because it implies, without substantial evidence, that Glucophage's main mechanism of action is to reduce insulin resistance. BMS has not adequately demonstrated that improving insulin sensitivity, one of three mechanisms listed in the PI, is metformin's major mechanism of action in lowering blood glucose. DDMAC refers BMS to our August 7, 1997, letter in which we outlined similar objections to violative materials and your August 19, 1997, response stating that BMS would discontinue the violative materials.

The claim "Glucophage decreases or stabilizes body weight..." is misleading because it implies a greater clinical effect on weight loss than has been demonstrated adequately. Further, the claim is inconsistent with the PI. As stated in the PI, "...body weight of individuals on Glucophage tends to remain stable or may even decrease somewhat."

In order to address these objections, DDMAC recommends that BMS take the following actions:

1. Immediately discontinue the use of this, and all other promotional materials for Glucophage that contain the same or similar violations. Such materials would include relevant materials also directed to consumers.

2. Provide to DDMAC, in writing, BMS' intent to comply with #1 above. Your response should be received by March 23, 1998.

3. Include a list of all violative promotional materials that will be discontinued and BMS' method for discontinuing their use.

DDMAC notes that this is the second letter notifying BMS of misleading presentations regarding Glucophage's mechanism of action. DDMAC will continue to monitor and evaluate promotional materials for Glucophage to determine if additional measures may be necessary to fully correct any continued dissemination of misleading messages.

If BMS has any questions or comments, please contact the undersigned by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-240, Rm 17B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds BMS that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID #6401 in addition to the NDA number.

Sincerely,

Mark W. Askine, R.Ph.
Regulatory Review officer
Division of Drug Marketing,
Advertising, and Communications