DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

AUG - 7 1997

**TRANSMITTED VIA FACSIMILE**

Steven J. Lenart
Assistant Director, Promotional Compliance
Bristol-Myers Squibb Company
P.O. Box 4500
Princeton, NJ 08543-4500

**RE: NDA# 20-357**
Glucophage (metformin HCl)
MACMIS ID # 5448

Dear Mr. Lenart:

Reference is made to Bristol-Myers Squibb Company's (BMS) May 16, 1997, submission of promotional materials on Form FDA 2253 for Glucophage (metformin HCl) tablets. The Division of Drug Marketing, Advertising and Communications (DDMAC) has reviewed the materials included in this submission, and has determined that the audiotape and script entitled "Meeting the Diabetes Challenge" (F5D048) are in violation of the Federal Food, Drug and Cosmetic Act and applicable regulations.

Specifically, this presentation implies that metformin is useful in a wider range of conditions than is provided in its approved product labeling (PI). For example, in the tape, Dr. DeFronzo describes the insulin resistance syndrome as "a cluster of metabolic and cardiovascular disorders that occur in people who have unaligned insulin resistance...." These disorders include obesity, hypertension, atherosclerosis, and the development of atherogenesis. Dr. DeFronzo goes on to state, "We all know that metformin is an excellent drug to lower the blood sugar. By lowering the blood sugar level, we will markedly decrease both microvascular and macrovascular complications... We also know that metformin, because it is an insulin sensitizer, will improve the insulin resistance."

These statements imply that metformin will have an effect on the clinical complications of the insulin-resistance syndrome, including obesity, hypertension, dyslipidemia, atherosclerosis, and the development of atherogenesis. They also imply that metformin will decrease the risk of myocardial infarction and stroke in addition to the decreasing the microvascular and microvascular complications associated with diabetes. However, metformin is neither indicated for treatment of

the insulin resistance syndrome and related complications, nor is it indicated to reduce the microvascular or microvascular complications associated with Type II diabetes.

Furthermore, Dr. DeFronzo states that metformin's "major mechanism of action is to improve...insulin sensitivity." This statement is misleading because BMS has not adequately demonstrated that improving insulin sensitivity, one of three mechanisms listed in the PI, is metformin's major mechanism of action. Additionally, the folder designed to hold the audiotape contains the claim "With Glucophage, we can *target* insulin resistance...." DDMAC considers this claim misleading because it implies that Glucophage's main mechanism of action is to reduce insulin resistance, which is not supported by adequate evidence.

Finally, Dr. DeFronzo states that "metformin has a rather powerful effect to lower the triglycerides..." and "Patients tend to lose weight...and it really does have a significant effect to lower the lipids." These claims are misleading because they imply a greater clinical effect on lipids and weight loss than has been demonstrated adequately. Again, the PI states that "...body weight of individuals on Glucophage tends to remain stable or may even decrease somewhat" and "Glucophage has a modest favorable effect on serum lipids...particularly when baseline levels were abnormally elevated...."

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.

2. Provide to DDMAC, in writing, BMS' intent to comply with #1 above. Your response should be received by August 21, 1997.

3. This response should include a list of all violative promotional materials and BMS' method for discontinuing their use.

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-40, Rm 17B-20, 5600 Fishers Lane, Rockville, MD 20857.

In all future correspondence regarding this particular matter, please refer to MACMIS ID #5448 in addition to the NDA number.

Sincerely,

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