DEPARTMEI : HEALTH & HUMAN SERVICES Pu ealth Service

Food and Drug Administration
Rockville MD 20857

TRANSMITTED VIA FACSIMILE

JAN - 7 1998

H. Oliver Stoutland, MD
Director, Promotional Compliance
Bristol-Myers Squibb Corporation
777 Scudders Mill Road
Plainsboro, NJ 08536

RE: **NDA 20-757**
Avapro (irbesartan) Tablets
MACMIS ID #6159

Dear Dr. Stoutland:

As part of its routine monitoring program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has become aware of promotional materials for Avapro (irbesartan) tablets by Bristol-Myers Squibb Corporation (BMS) that violate the Federal Food, Drug and Cosmetic Act and its regulations. Reference is made to the following specific materials submitted under cover of Form FDA 2253: brochures (B2-A002, B2-A003, B2-A004, B2-B017), and journal ads (B2-K005, B2-K002). DDMAC has reviewed these materials for Avapro and has determined that they promote Avapro in a manner that is considered false or misleading because they are lacking in fair balance, or otherwise misleading.

In these materials, BMS describes the safety profile for Avapro as "placebo-level." In letters from DDMAC, dated October 9, 1997, and October 16, 1997, comments were made on proposed launch materials for Avapro. In these letters, BMS was informed that DDMAC would object to the claim "placebo-level," since it would misrepresent Avapro's safety profile. DDMAC considers that this claim implies that the side effect profile for Avapro is the same as placebo, not similar to placebo as described in Avapro's approved product labeling. As stated in the above referenced letters, placebo-controlled trials have demonstrated that several side effects occurred at higher incidence in patients receiving Avapro versus those receiving placebo. In addition, use of Avapro during pregnancy may cause fetal injury or death, a side effect not associated with the use of a placebo. Therefore, DDMAC continues to consider the claim "placebo-level" to be false or misleading, since it misrepresents Avapro's safety profile.

Promotional materials must present information about the risks associated with the use of the drug in a manner reasonably comparable to that of claims concerning the drug's efficacy or safety. In general, these claims should be accompanied by information about the most serious (i.e., boxed warning for use in pregnancy) and the most common adverse events associated with the use of the drug. The most common adverse events should be presented, even if their rates of

occurrence are equal to, or less than placebo. Furthermore, promotional materials claiming incidence rates of adverse events to be similar to placebo necessitate the addition of sufficient contextual information, clarifying which adverse events occur at a higher incidence with the drug.

In these promotional materials, although BMS references the boxed warning for use in pregnancy and presents the five adverse events occurring at higher incidences with Avapro versus placebo with their respective percentages, BMS fails to present the most common adverse events associated with Avapro's use. Once again, reference is made to page 2 of the letter from DDMAC, dated October 9, 1997, that stated "...BMS should qualify claims of Avapro's tolerability by reporting the most common side effects, as well as the side effects occurring in at least 1% of patients treated with Avapro and at a higher incidence versus placebo, with their respective incidence rates and placebo rates." Therefore, DDMAC reiterates that these materials are lacking in fair balance, or are otherwise misleading for claims where Avapro's safety profile is compared to placebo, because the risk information presented concerning the tolerability of Avapro is insufficient.

BMS should immediately cease distribution of these and other similar promotional materials for Avapro that contain the same or similar claims or presentations. BMS should submit a written response to DDMAC on or before January 22, 1998, describing its intent and plans to comply with the above.

BMS should direct its response to 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, Maryland 20857. DDMAC reminds BMS that only written communications are considered official.

In all correspondence regarding this particular submission, please refer to MACMIS ID #6159, in addition to the NDA number.

Sincerely,

Janet Norden, MSN, RN
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications