DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

FOI

TRANSMITTED VIA FACSIMILE

SEP 23 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 # 6799

Dear Dr. Stoutland:

Reference is made to Bristol-Myers Squibb Company's (BMS) letter, dated July 15, 1998, in response to a letter from the Division of Drug Marketing, Advertising and Communications (DDMAC), dated July 2, 1998. DDMAC's letter concerned the alleged dissemination of a homemade promotional piece by or on behalf of BMS, that promoted Avapro (irbesartan) tablets in violation of the Federal Food, Drug and Cosmetic Act (Act) and its regulations. DDMAC requested that BMS investigate the extent to which this homemade piece was used to promote Avapro, and the number of health care professionals who received this piece.

In your letter, you described that this homemade promotional piece was distributed by one sales representative to approximately 40-50 physicians in the Grand Junction, Colorado area beginning in December 1997 through January 5, 1998. Your letter also described BMS' policy for prohibiting dissemination of homemade materials by your sales force, and specified the corrective actions taken to ensure that this activity will not continue.

DDMAC has reviewed this promotional piece and has determined that it is false or misleading because it contains misrepresentations of Avapro's safety and efficacy, unsubstantiated comparative claims, and is lacking in fair balance.

Misrepresentations of safety and efficacy

- In this "homemade" promotional piece, BMS claims that Avapro "has placebo-level side effects at every dose." In letters from DDMAC, dated October 9, 1997, October 16, 1997, and January 7, 1998, we objected to this claim because it misrepresents Avapro's safety profile. DDMAC reiterates that this claim minimizes the occurrence and seriousness of the adverse reactions associated with Avapro's use, and is therefore, false or misleading.

- The claim "can be used in virtually any patient group (pregnancy and hypersensitive are the

only contraindications)," overstates the safety of Avapro's use. For example, the approved product labeling (PI) for Avapro cites a precaution for use in patients with impaired renal function, as well as a recommendation for dosage adjustment in volume- or salt-depleted patients. Failure to disclose this important risk information is misleading because it misrepresents Avapro's safety profile.

- BMS presents the claim "controls 75% of patients as first line, monotherapy agent," in this promotional piece. DDMAC considers this statement to overstate Avapro's effectiveness by omission. This efficacy rate should be accompanied by sufficient context to adequately describe the clinical trial(s) from which this result was derived. Without context, this claim is misleading because it overstates the efficacy rate of Avapro monotherapy.

- The claim "no known drug-drug interactions" implies that Avapro can be safely administered with other drug products, without concern for potential drug-drug interactions. However, the PI for Avapro states that no drug-drug interactions have been found in interaction studies with four drugs (hydrochlorothiazide, digoxin, warfarin, and nifedipine). Therefore, this claim is misleading because it lacks necessary context to clarify the limitations of known drug-drug interactions.

- BMS' claim that Avapro "showed discontinuation rates in controlled studies less than placebo, 3.3 AVAPRO, 4.5 placebo, (n=2,606)" implies that Avapro is not associated with any adverse reactions. However, the side effect profile for Avapro includes several side effects occurring at higher rates in patients receiving Avapro versus those receiving placebo (i.e., diarrhea, dyspepsia/heartburn, musculoskeletal trauma, fatigue, and upper respiratory infection). Therefore, this claim is misleading because it minimizes the occurrence and seriousness of the adverse events associated with Avapro, and fails to provide risk information to balance the claim.

Unsubstantiated comparative claims

- BMS' claim that Avapro is "the first and only antihypertensive to completely block angiotensin II at the AT_1 receptor" implies superiority over other existing angiotensin II receptor blockers (ARBs). However, the clinical significance of complete blockade of angiotensin II is unknown. Therefore, DDMAC considers this claim to be false or misleading because it is not supported by substantial evidence.

- The claim "has a longer half-life than all other ARB's, 11-15 hours which insures full 24 hour effect," implies that the other ARBs, do not provide 24-hour blood pressure reduction. However, other ARBs have demonstrated 24-hour duration of action with once daily dosing. Therefore, the implication that a pharmacokinetic measure (i.e., longer half-life) provides an advantage in clinical effect over other products is misleading because it is not supported by substantial evidence.

- BMS presents the claim "this is an ARB that works!!" in this promotional piece. This statement suggests that all other ARBs do not "work" to reduce blood pressure. However, other ARBs have demonstrated efficacy in the treatment of hypertension. Therefore, BMS has misbranded Avapro by disparaging the efficacy of other ARBs.

Lacking in fair balance

Overall, this promotional piece is lacking in fair balance with respect to the content and presentation of risk information related to the use of Avapro. 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. In general, claims should be accompanied by information about the most serious and most common adverse events associated with the use of the drug.

Although this piece contains numerous claims for the efficacy and safety of Avapro, information concerning the warnings, precautions, or adverse events associated with Avapro's use are not presented. In addition, several claims comparing Avapro to placebo (see "Misrepresentations of safety and efficacy" above) are not balanced by contextual information, clarifying which adverse events occur at higher incidences with Avapro than placebo.

Furthermore, BMS states, in the context of a claim, that pregnancy is a contraindication for Avapro's use. This disclosure fails to adequately address the serious consequences of using Avapro during pregnancy. Information from the PI's boxed warning concerning the risk of fetal injury or death should be prominently disclosed in all promotional materials.

Therefore, since Avapro has significant risks associated with its use, especially during pregnancy, this promotional piece is lacking in fair balance, or otherwise misleading because it fails to address these risks. Finally, the promotional piece is in violation of the Act because it was not accompanied by the PI for Avapro.

DDMAC has reviewed your response and actions taken in response to the dissemination of this violative promotional piece. Although DDMAC does not wish to comment on the internal processes of BMS, we are concerned because this is not the first instance of violative "homemade" promotional materials being disseminated by BMS sales representatives.

In light of actions taken by BMS, DDMAC considers this matter closed. However, DDMAC will continue to closely monitor this issue. If you have any further questions or comments, please direct them 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, 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 #6799 in addition to the NDA number.

Sincerely,

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

cc: Gregory Torre, Ph.D., J.D.
Senior Director, Drug Regulatory Affairs
Sanofi Pharmaceuticals, Inc.
90 Park Avenue
New York, NY 10016