DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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TRANSMITTED VIA FACSIMILE

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

MAR 25 1998

RE: **NDA 20-757**
Avapro (irbesartan) Tablets
MACMIS ID #6270

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 leaflet (B2-A010R) submitted under cover of Form FDA 2253. DDMAC has reviewed this material for Avapro and has determined that it promotes Avapro in a manner that is false and/or misleading, because it overstates Avapro's efficacy and makes superiority claims that are not supported by substantial evidence.

Misleading Representations of Efficacy

In this leaflet, BMS describes the results of an 8-week, placebo-controlled, double blind study, comparing once-daily doses of Avapro 150 mg, Avapro 300 mg, losartan 100 mg, and placebo in patients with mild-to-moderate hypertension. Although BMS prominently presents the efficacy data as change in seated trough diastolic blood pressure (SeDBP) at 8 weeks, BMS does not present the rates of patients achieving normalization (defined as trough SeDBP < 90 mmHg) or response (defined as trough SeDBP < 90 mmHg or a reduction of trough SeDBP $\geq$ 10 mmHg) for this trial. DDMAC considers that this presentation implies that all patients achieved the presented reductions in blood pressure. However, this clinical trial demonstrated only a 52% normalization rate and a 63% response rate at week 8 with the highest dose of Avapro (300 mg). DDMAC considers that presentation of efficacy results in this manner implies that Avapro is more effective than demonstrated in clinical trials, and therefore is false and/or misleading.

Unsubstantiated Superiority Claims

In addition, BMS displays graphically, and in the study results section of this leaflet, that "[t]he maximum once-daily dose of Avapro (300 mg) provided a statistically significant greater antihypertensive effect vs. the maximum recommended once-daily dose of losartan (100 mg)." DDMAC considers that this claim implies that Avapro possesses a superior antihypertensive

effect when compared to losartan. However, this claim is based on a single study, the results of which have not been replicated or demonstrated in other adequate and well-controlled, head-to-head clinical trials. In general, DDMAC considers two adequate, well-controlled clinical studies as substantial evidence. Thus, DDMAC considers this to be a superiority claim that is not supported by substantial evidence, and therefore, is false and/or misleading.

BMS should immediately cease distribution of this and any other promotional materials for Avapro that contain the same or similar claims or presentations. BMS should submit a written response to DDMAC on or before April 8, 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 #6270, in addition to the NDA number.

Sincerely,

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