DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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TRANSMITTED VIA FACSIMILE

MAY 28 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 #6617

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.

Previously, in a letter dated March 25, 1998, DDMAC objected to a promotional (B2-A010R) for Avapro that contained claims that overstated Avapro's efficacy and made superiority claims that were not supported by substantial evidence. In this leaflet, BMS described 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. The clinical trial demonstrated that the maximum once-daily dose of Avapro was superior in reducting seated diastolic blood pressure (SeDBP) versus the maximum once-daily dose of losartan. DDMAC objected to presentation of this data because the results had not been replicated or demonstrated in other adequate and well-controlled, head-to-head clinical trials. In a letter, dated April 6, 1998, BMS responded by providing DDMAC with data from a second clinical trial that supported the results of the clinical trial presented in the leaflet. In our letter, dated May 13, 1998, DDMAC agreed that the two clinical trials supported the claim that the highest approved dose of Avapro, given once a day, is superior in reducing SeDBP versus the highest approved dose of losartan, given once a day. However, DDMAC recommended that BMS prominently disclose that there is no evidence that Avapro 300 mg, given once a day, is superior to losartan 50 mg, given twice a day.

Recently, DDMAC has become aware of promotional materials for Avapro that contain claims related to the two clinical trials described above. Reference is made to the following promotional materials submitted under cover of Form FDA 2253: (B2-A018), (B2-K012), (B2-A019) and (B2-B021). DDMAC has reviewed these materials and

has determined that they promote Avapro in a manner that is false or misleading because they contain unsubstantiated representations of superiority, overstatements of efficacy, graphic misrepresentations, and unsubstantiated claims for enhanced patient compliance.

Unsubstantiated representations of superiority

In these promotional materials, BMS presents artwork in which Avapro is represented as a and other antihypertensive drugs as The text accompanying this artwork includes the following claims: "An ARB with real power," and "Avapro: an ideal profile for first-line therapy." This artwork and these claims imply that Avapro is superior to other antihypertensive therapies, including other angiotensin II receptor blockers (ARBs). Although, as stated above, BMS has data to support that the highest approved once-daily dose of Avapro is superior in reducing SeDBP, to the highest approved once-daily dose of losartan, Avapro has not demonstrated superiority over any other antihypertensive drugs. Therefore, DDMAC would consider this artwork and these claims to be false or misleading because they are not based on substantial evidence.

In the BMS presents a headline stating "[s]uperior antihypertensive effect with Avapro regimen" and a graph depicting the results of a comparison of mean change in SeDBP at 12 weeks for an Avapro regimen [including combination therapy with hydrochlorothiazide (HCTZ)] and a losartan regimen (including combination therapy with HCTZ). The resultant p value for the Avapro regimen is statistically significant at $p<0.002$, implying superior efficacy of the Avapro regimen over the losartan regimen. However, this study was not designed to adequately evaluate Avapro/HCTZ combination therapy versus losartan/HCTZ combination therapy, and these results have not been replicated in other adequate, well-controlled clinical trials. Therefore, DDMAC considers this presentation to be false or misleading because it represents a superiority claim that is not supported by substantial evidence.

Furthermore, BMS presents the claim "[c]omparison of usual starting and maximum QD dose regimens of Avapro and losartan" as the title for the graph depicting the combination regimens. DDMAC considers this title to be false and/or misleading because the maximum QD dosing regime for losartan/HCTZ combination therapy was not compared in this clinical trial.

In addition, BMS presents the claim "an ideal profile for first-line therapy" on the page with the graph depicting combination therapy regimens. In addition to this claim representing an unsubstantiated superiority claim, DDMAC also considers it to be misleading because combination therapy is not recommended as first-line therapy.

Overstatements of efficacy

In these promotional materials, BMS presents several claims for Avapro's antihypertensive effect, including: "the power to control," "antihypertensive power at all doses," "real power at the starting dose of 150 mg once daily," and "prescribe starting dose of 150 mg once daily, expect hypertension control in the patients you treat." These claims imply absolute capability to control blood pressure at any dose of Avapro. However, based on blood pressure response and normalization rates, these claims overstate Avapro's demonstrated efficacy. For example, in the study described above in DDMAC's March 25, 1998 letter, the normalization and response rates for Avapro at the primary endpoint of the study (week 8), were only 52% and 63%, respectively for the highest dose of Avapro. In addition, DDMAC considers claims concerning starting dose "power" to be particularly overstated. For example, in the legend of the graph presented in the journal ad, BMS presents the percent of patients who required titration to a higher dose of Avapro at 8 weeks to be 53%. However, on page 4 of the ad, BMS claims "real power at the starting dose of 150 mg once daily." With over half of the patients failing to achieve adequate blood pressure reduction at the starting dose of Avapro, a practitioner should not "expect" hypertension control, especially in those receiving the starting dose of Avapro. Therefore, DDMAC considers these claims to be misleading because they overstate the efficacy of Avapro. As stated in DDMAC's letter, dated May 13, 1998, in promotional pieces where claims are presented concerning comparative response rates or expected response to therapy, DDMAC considers exclusion of patient response rates to be misleading.

Graphic misrepresentations

In the (page 4) and in the (pages 4-5), BMS presents efficacy claims for Avapro in graphs. However, these graphs lack sufficient context concerning the source of the data. Graphs should clearly, fairly, and accurately depict study results. Context discussing the study should be placed directly adjacent to the graph, and should expressly refer to the graph. This context should include information about the design of the study

In BMS' presentation, it is not apparent how the results displayed on the graph were derived. Therefore, these graphs imply greater efficacy in a broader range of patients than demonstrated in the clinical trials. Thus, DDMAC considers that these graphs misrepresent study results because they lack context to adequately describe the studies from which the results were derived.

Unsubstantiated claim for enhanced patient compliance

In the and the BMS claims "...power to enhance compliance" with a graph depicting discontinuation rates of patients on placebo versus Avapro therapy. However, this tolerability data and its relationship to patient compliance has not been evaluated in clinical trials. Patient compliance may be influenced by a number of factors, including patient variables economic variables, drug-related variables etc. Therefore, DDMAC considers this claim to be false or misleading, since it has not been supported by adequate evidence.

BMS should immediately cease distribution of these 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 June 11, 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 #6617, in addition to the NDA number.

Sincerely,

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