DEPARTMENT OF HEALTH & HUMAN SERVICES

FOI

Food and Drug Administration
Rockville MD 20857

TRANSMITTED VIA FACSIMILE

Stephen J. Lenart
Assistant Director, Regulatory Sciences
Bristol-Myers Squibb Company
PO Box 4500
Princeton, NJ 08543-4500

MAR 31 1999

RE: **NDA 20-757**
Avapro (irbesartan) Tablets
MACMIS ID # 7423

Dear Mr. Lenart:

As part of our routine monitoring program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has become aware of promotional materials for Avapro (irbesartan) tablets, disseminated by Bristol-Myers Squibb Company (BMS), that violate the Federal Food, Drug and Cosmetic Act and its regulations. Reference is made to a brochure (B2-A041) and a journal ad (B2-K017) submitted under cover of Form FDA 2253. DDMAC has reviewed these materials for Avapro and has determined that they promote Avapro in a manner that is false or misleading, and lacking in fair balance. Although we are citing these selected materials, we note that the same or similar claims or representations are presented in other promotional materials disseminated for promotion of Avapro. Our comments should be applied to all other promotional materials for Avapro.

Overstatement of Efficacy

Comparison to losartan

In the brochure, you present superiority claims for Avapro over Cozaar (losartan potassium)[1] based on two clinical trials[2,3] that appear to support a claim that the highest

1. Cozaar (losartan potassium) tablets is a product of Merck & Co., Inc.

2. Kassler-Taub K, Littlejohn T, Elliott W, et al. Comparative efficacy of two angiotensin II receptor antagonists, irbesartan and losartan, in mild-to-moderate hypertension. *American Journal of Hypertension*. 1998, 11(4): 445-453.

3. Oparil S, Guthrie R, Lewin AJ, et al. An elective-titration study of the comparative effectiveness of two angiotensin II-receptor blockers, irbesartan and losartan. *Clinical Therapeutics*. 1998, 20(3): 398-409.

approved dose of Avapro, given once a day, is superior in reducing sitting trough diastolic blood pressure (DBP) versus the highest approved dose of losartan, given once a day. However, your presentation of the results of these clinical trials blatantly overstates the results, distorting and misrepresenting the differences between these drug products.

The resultant mean change from baseline trough DBP (mmHg) at the primary endpoints of the studies for trial #1 and #2 respectively, were Avapro 300 mg QD (-11.7 mmHg) and losartan 100 mg QD (-8.7 mmHg), and Avapro 150 mg and 300 mg QD (-10.2 mmHg) and losartan 50 mg and 100 mg QD (-7.9 mmHg). In large, colorful arrows next to the text describing the results of the clinical trials, you present that Avapro was superior to losartan by 34% for trial #1 and 29% for trial #2. However, this percentage represents a difference between Avapro and losartan of 3 mmHg and 2.3 mmHg respectively for the two trials. This presentation is misleading because it grossly overstates the difference between the treatment groups, implying that Avapro is more effective than demonstrated in these clinical trials.

Furthermore, your presentation of the Avapro racecar "beating" the Cozaar racecar on the front cover of the brochure, as well as the headers that state that "there's only one proven winner vs. losartan: Avapro," and "Avapro – the only ARB with proven superior blood pressure reduction vs. Cozaar (losartan) in two head-to-head studies" are also misleading. These claims and presentations imply that at any dose, or dosing regimen, Avapro was superior to losartan. However, these clinical trials do not support this implication. Although, on page 3, you present the efficacy results in faint text, and a tiny type size disclaimer that "a comparison between QD Avapro and BID losartan was not made in these studies," these presentations are not adequate to correct the misleading impressions made by the pictures and headers.

In the journal ad referenced above, you present similar claims of superiority for Avapro over losartan (e.g., "Real power over losartan," and "the only ARB with two head-to-head clinical studies demonstrating superior efficacy") without providing any contextual information about the clinical trials to qualify these claims. As stated above, this presentation is misleading because it overstates the results of the clinical trials, implying a greater efficacy for Avapro than demonstrated by these clinical trials.

Efficacy claims based on inadequate evidence

On page 5 of the brochure, you present a graph and the claim that "Avapro 150 mg QD provides 24-hour blood pressure reduction." Immediately following this presentation, you present a graph and the claim that "85% of Avapro patients are taking 150 mg, the recommended starting dose." This claim implies that 85% of patients are adequately controlled on the starting dose of Avapro (i.e., 150 mg). However, this claim is not derived from adequate and well-controlled clinical trials assessing Avapro's response

rates. In fact, clinical trials evaluating these response rates demonstrated a much lower ability to control blood pressure than 85%, even before placebo-correction. Therefore, these claims are misleading because they are not based on adequate evidence and they overstate the response rates to Avapro, implying greater efficacy than demonstrated by substantial evidence.

Misrepresentations of mechanism of action/pharmacokinetic information to imply clinical superiority over other ARBs

Throughout this brochure, you present the question "Are all ARBs the same?" followed by claims that suggest that Avapro is superior to the other approved ARBs. For example, on page 4 of the brochure, you present the following claims:

- "Avapro: the ARB with 100% blockade at the AT_1 receptor site"
- A graph comparing the "Degree and duration of ANG II blockade: comparison of Avapro, losartan and valsartan[4]"
- "Degree + duration = sustained ANG II blockade with Avapro"
- Across approved product labeling (PI) comparisons of the half-lives of Avapro and four other approved ARBs

These claims and representations imply that Avapro possesses clinical advantages due to its receptor binding ability and its half-life duration. However, the relationship between receptor binding affinity and clinical effect is unknown. Furthermore, the clinical significance of Avapro's 11-15 hour half-life is unknown. Therefore, these claims and representations are misleading because they suggest clinical effect, including implying clinical superiority over other ARBs, when no such clinical relevance has been demonstrated by substantial evidence. Furthermore, these misleading claims and representations are not corrected by the inclusion of your small type size disclaimer that the clinical significance is unknown, and this disclaimer does not correct the unsubstantiated superiority claims over the other ARBs.

Lack of fair balance

Promotional materials are false, lacking in fair balance or otherwise misleading if they contain a representation or suggestion, not approved in the labeling, that a drug is more effective, safer, or useful in a broader range of conditions or patients than has been demonstrated by substantial evidence or substantial clinical experience. Furthermore, promotional materials are false or misleading, lacking in fair balance or otherwise misleading if they fail to present the information relating to the contraindications, warnings, precautions, and side effects associated with the use of the drug with a prominence and readability reasonably comparable to the presentation of information relating to the effectiveness of the drug. In reviewing the presentation of such

4. Diovan (valsartan) capsules is a product of Novartis Pharmaceuticals Corporation.

information, techniques likely to achieve emphasis are taken into account. These include typography, layout, contrast, headlines, paragraphing, white space, etc. In these materials, you have failed to present risk information in a reasonably comparable manner, as follows:

- Throughout the brochure, you present bold, bulleted, colorful claims and representations promoting the efficacy of Avapro. However, risk information is presented in small type size and/or thin lined font at the bottom of the pages. For example, on page 5, the information from the boxed warning in Avapro's PI concerning the risk of fetal injury or death if Avapro is used during the second or third trimesters in pregnancy is presented in small, continuous text at the bottom of the page. In even smaller text, the warning for the risk of hypotension when Avapro is used in volume depleted patients is presented. This presentation is not adequately prominent to balance the efficacy claims, nor to convey these risks to prescribers.

- On page 6 of the brochure, you present a graph depicting, "efficacy results regardless of age, race or gender." However, the context to qualify Avapro's lower efficacy in black patients is presented as a tiny type size footnote, remote from the claim. This footnote is separated from the claim it qualifies and lacks prominence.

- On pages 6 and 7 of the brochure, you prominently present claims regarding the safety profile of Avapro. For example, the large type headers "Avapro: proven tolerability and safety at all doses," "tolerability similar to placebo," and "a favorable safety profile" are presented over graphs and bulleted claims promoting the safety profile of Avapro. However, the important warning for use in pregnancy and the only information presented concerning the adverse events associated with Avapro's use, are presented as a running text paragraph at the bottom of page 6. This presentation is inadequate to balance the presentation of the numerous efficacy and safety claims contained in this brochure, and is not presented in a reasonably comparable manner with respect to prominence.

- On page 7 of this brochure, the claim that "no dosage adjustment in the elderly, or in patients with renal or hepatic impairment" implies that Avapro can be administered to these patients without concern for dose-related adverse events. However, you have failed to balance this claim with the important risk information in the Warning section of the PI concerning excessive hypotension in patients who are volume- or salt-depleted, and information from the Precautions section of the PI concerning the risks associated with Avapro in patients with renal impairment.

- In the journal ad identified above, the only risk information presented to balance the superior efficacy claims is the boxed warning from the PI regarding use in pregnancy. Avapro is associated with other risks and adverse events. This journal ad is lacking in fair balance because it fails to adequately or prominently present the risks associated with Avapro therapy.

BMS should immediately cease distribution of these promotional materials, and all 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 14, 1999, describing its intent and plans to comply with the above. In your letter, we request that you include a list of all promotional pieces that were discontinued, and the discontinuation date.

You should direct your 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, 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 #7423 in addition to the NDA number.

Sincerely,

/S/

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

CC:
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