DEPARTMENT OF HEALTH & HUMAN SERVICES

FOI

Food and Drug Administration
Rockville MD 20857

TRANSMITTED VIA FACSIMILE

APR 16 1999

Heidi C. Reidies
DRA Associate Director
Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
P.O. Box 368
Ridgefield, Connecticut 06877

RE: NDA #20-850
Micardis (telmisartan) Tablets, 40 mg and 80 mg
MACMIS ID #7853

Dear Ms. Reidies:

As part of its routine monitoring program, the Division of Drug Marketing, Advertising and Communications (DDMAC) has become aware of promotional materials for Micardis (telmisartan) tablets, disseminated by Boehringer Ingelheim Pharmaceuticals, Inc. (BI), that are in violation of the Federal Food, Drug, and Cosmetic Act and its implementing regulations. Reference is made to a journal ad (MC-6923) and a sales aid (MC-6924), submitted under cover of Form FDA 2253 on March 30, 1999. DDMAC has determined that BI failed to submit these, and other materials for Micardis, at the time of initial use, in violation of the post-marketing requirements for prescription drugs. Furthermore, DDMAC has reviewed these materials and has determined that they are false or misleading, and lacking in fair balance.

Failure to submit post-marketing reports at the time of initial use

The regulations for post-marketing reports for prescription drug advertising and labeling require that sponsors submit promotional materials to the FDA, under cover of Form FDA 2253, at the time of initial dissemination. On February 5, 1999, you submitted to DDMAC, under cover of Form FDA 2253, promotional materials for Micardis, identified as telemarketing script copy (MC-6966), trade press release (MC-7017T), and pharmacy sell sheet (MC-6930). In your cover letter, you stated that these materials were initially used in December 1998, but were discontinued after receiving our comments on launch materials for Micardis, dated December 11, 1998. We note that these pieces contained the same or similar claims as your draft launch materials that you sent to DDMAC for comment on November 25, 1998. Therefore, although these materials were in use since December 1998, and during the time of our review of draft materials, you failed to submit them until February 5, 1999. As stated above, this is a violation of the post-marketing reporting requirements.

In addition, reference is made to your March 10, 1999, request for comments on a draft sales aid and journal ad, and our March 23, 1999, letter in response to that request. In our letter, we stated that dissemination of these draft promotional materials would be false or misleading and lacking in fair balance. Reference is also made to a telephone conversation between Heidi Reidies (BI) and Janet Norden (DDMAC) on March 25, 1999, during which you stated that the identical promotional materials that were sent to DDMAC for comment on March 10, 1999, were currently in use for promotion of Micardis. As above, although these materials were in use simultaneously with your request for comment on their "draft" form, you failed to submit them until March 30, 1999, in violation of the post-marketing reporting requirements.

Furthermore, in your April 2, 1999 letter, requesting comments on revised proposed promotional materials for Micardis, you stated that you intend to continue using the March 30, 1999 version of the sales aid and journal ad. We have reviewed the March 30, 1999 version of the sales aid and journal ad and have determined that they are false or misleading and lacking in fair balance. Our specific objections follow:

Misleading representations of efficacy

You present the header that "the time is right for an ARB like Micardis" over pages that contain claims regarding Micardis' efficacy and safety, including patient response rates, renal safety profile, tolerability profile, and drug interaction information. This header implies that other available angiotensin II receptor blockers (ARBs) do not possess similar characteristics, and that Micardis therapy is superior, when compared to them. However, Micardis therapy has not been shown to be superior to other available ARBs. Therefore, this claim is misleading because it implies superiority over other ARBs, which has not been demonstrated by substantial evidence.

In addition, you present two pie charts depicting response rates for "Micardis monotherapy," and for a "Micardis-based regimen." However, the contextual information necessary to interpret these pie charts is lacking in both prominence and content. Since your presentation of the "Micardis monotherapy" response rate is not corrected for placebo-response, and the corresponding 29% placebo-response is not presented with comparable prominence to the pie chart, your presentation implies that Micardis is more effective than has been demonstrated. Furthermore, your presentation of contextual information accompanying the "Micardis-based regimen" pie chart inadequately addresses the information necessary to interpret this result. In addition to the information presented, it is misleading to omit the definition of the duration of the "long-term extension study," and to fail to disclose the percentage of responders to Micardis monotherapy, and to Micardis plus hydrochlorothiazide therapy. Therefore, these presentations of response rates are misleading because they overstate the efficacy of Micardis, and fail to provide adequate prominence and content to the important contextual information relating to the pie charts.

In a graph, you present the pooled observed mean change from baseline blood pressure response (mm Hg) for Micardis versus placebo. However, the placebo responses are reversed for diastolic and systolic blood pressure (i.e., the placebo responses should be –2.2 mm Hg for diastolic and –0.3 mm Hg for systolic blood pressure). Therefore, the graph inaccurately depicts the results of the clinical trials.

Misleading use of pharmacokinetic data to imply clinical effect

In these promotional materials, you present the claim "24-hour half-life for once-daily dosing." This claim implies that the duration of clinical effectiveness is due to Micardis' half-life duration. This suggestion is further strengthened by presentation of this claim under a header that states "delivers effective blood pressure control." However, the terminal elimination half-life does not necessarily predict duration of clinical effectiveness. Therefore, this presentation is misleading because it uses pharmacokinetic data to imply clinical effect, when no such clinical significance has been demonstrated by substantial evidence.

Misleading representations of safety and tolerability

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. Claims promoting the efficacy of a drug should be accompanied by information about the most serious and the most common side effects associated with the use of the drug. When compared to the bolded, bulleted, colorful presentation of efficacy claims for Micardis in this sales aid and journal ad, the information relating to the risks associated with Micardis are not presented with a reasonably comparable prominence and readability. Therefore, these materials are lacking in fair balance.

In addition, you present the claim that Micardis is associated with a "tolerability profile similar to placebo." However, the approved product labeling (PI) for Micardis lists adverse events that occurred at a higher incidence with Micardis than with placebo. For this reason, in addition to presentation of the most serious and most common side effects, this claim is misleading without the inclusion of sufficient contextual information, clarifying which adverse events occur at a higher incidence with the drug versus placebo (with their respective incidence rates and placebo rates). However, in these multi-page pieces, this risk information, or a prominent reference to where this information can be located, is not presented with the claim. Therefore, this claim is misleading because it misrepresents Micardis' safety profile.

In the sales aid, you present that both Micardis and placebo are associated with a 0% incidence rate of hypokalemia. This presentation implies that Micardis is never associated with hypokalemia. However, hypokalemia did occur in 0.3% of patients receiving Micardis and 0.3%

of patients receiving placebo. Therefore, presentation of a 0% incidence rate for hypokalemia is misleading because it implies that Micardis is safer than demonstrated by substantial evidence.

BI should immediately cease distribution of these and other similar promotional materials for Micardis that contain the same or similar claims or presentations. BI should provide a written response to DDMAC, on or before April 30, 1999, describing its intent and plans to comply with the above. In your letter, we request that you include the following:

1) A list of all promotional pieces that were discontinued and the discontinuation date.

2) A plan that will ensure that all promotional materials are submitted to the Agency at the time of initial dissemination.

If there are additional questions or comments, please contact 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 BI that only written communications are considered official.

In all correspondence regarding this particular matter, please refer to MACMIS ID #7853 in addition to the NDA number.

Sincerely,

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