DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Brian A. Walter, Ph.D.
Associate Director, Drug Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877-0368

RE: NDA # 20-850 & 21-162
Micardis® (telmisartan) Tablets
Micardis® HCT (telmisartan and hydrochlorothiazide) Tablets
MACMIS ID # 12589

Dear Dr. Walter:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a sales aid with pocket insert card (MC-9104 and MC-9104A) for Micardis® (telmisartan) Tablets and Micardis® HCT (telmisartan and hydrochlorothiazide) Tablets submitted by Boehringer Ingelheim Pharmaceuticals, Inc. (Boehringer Ingelheim) under cover of Form FDA 2253. The sales aid is false or misleading because it contains unsubstantiated effectiveness and superiority claims and omits information on the risks associated with Micardis and Micardis HCT, and, therefore, misbrands the drugs in violation of section 502(a) of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. § 352(a).

Background

According to the FDA-approved labeling (PI), Micardis and Micardis HCT are angiotensin II receptor antagonists. Micardis is indicated for the treatment of hypertension, alone or in combination with other antihypertensive agents. Micardis HCT is indicated for the treatment of hypertension. It is a fixed dose combination and is not indicated for initial therapy. Both drugs are contraindicated in patients who are hypersensitive to any component. MICARDIS HCT is also contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

The PIs for Micardis and Micardis HCT include the following Boxed Warning regarding use in pregnancy:

USE IN PREGNANCY
When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus.
When pregnancy is detected, Micardis®/Micardis® HCT (telmisartan/hydrochlorothiazide) tablets should be discontinued as soon as possible.
See WARNINGS: Fetal/Neonatal Morbidity and Mortality

Additional information on the risks of using the drugs in pregnancy appears in the Warnings section of their respective PIs. The PI for Micardis contains the following additional warning:

> **Hypotension in Volume-Depleted Patients**
> In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients (e.g., those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of therapy with Micardis® tablets. This condition should be corrected prior to administration of Micardis tablets, or treatment should start under close medical supervision with a reduced dose.
>
> If hypotension does occur, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

The PI for Micardis HCT also includes a warning about hypotension in volume-depleted patients. It also contains the following additional warnings about the hydrochlorothiazide component:

> Thiazides cross the placental barrier and appear in cord blood. There is a risk of fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.
> . . .
>
> *Hepatic Impairment:* Thiazide diuretics should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.
>
> *Hypersensitivity Reaction:* Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.
>
> *Systemic Lupus Erythematosus:* Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.
>
> *Lithium Interaction:* Lithium generally should not be given with thiazides (see PRECAUTIONS, Drug Interactions, Hydrochlorothiazide, *Lithium)*.

Unsubstantiated Effectiveness Claim

The sales aid, entitled "EARLY MORNING RISK," includes a picture, on the cover, of a man sleeping in a bed that is sitting on top of train tracks as the sun is rising. Along with this picture, the sales aid includes the following claims:

> Morning blood pressure surge (MBPS) has been linked to a 22% rise in stroke risk. - *Kario et al*. Circulation. *2003*.
>
> Powerful BP [blood pressure] protection even in the risky early morning hours
>
> Good Morning. Micardis.
>
> Early Morning BP Protection

The sales aid thus claims that, by decreasing blood pressure and controlling the morning blood pressure surge, Micardis will reduce the risk of stroke even during the risky early morning hours. We are not aware of substantial evidence or substantial clinical experience demonstrating that Micardis is effective in reducing the risk of stroke at any time, including the morning hours. The references provided for these claims do not provide substantial evidence or substantial clinical experience. For example, the Kario[1] study, cited in the sales aid to support the claims, was a retrospective epidemiologic analysis that did not study the effect of any intervention on outcomes such as morbidity or mortality. Similarly, the Lacourciere study[2], which compared blood pressure effects of telmisartan and amlodipine, did not measure improvements in outcomes such as morbidity or mortality. We are not aware of other data constituting substantial evidence or substantial clinical experience to support this claim.

Unsubstantiated Superiority Claims

Your sales aid includes a graphic demonstrating reductions in systolic and diastolic blood pressure for Micardis and Norvasc based on ambulatory blood pressure monitoring (ABPM), accompanied by the statement, "Delivers proven BP reductions **vs Norvasc® (amlodipine)** 5 mg and 10 mg – the most prescribed calcium channel blocker." The diastolic blood pressure reductions presented for Micardis and Norvasc, -12.1 mm HG and -8.7 mmHg respectively, with a $P<0.05$ for Micardis vs Norvasc, suggest that Micardis is superior to Norvasc.

We are not aware of substantial evidence or substantial clinical experience demonstrating that Micardis is superior to Norvasc. The reference provided for this claim does not provide substantial evidence or substantial clinical experience. The majority of patients (47/78 or 60%) in the Norvasc arm of the Lacourciere study did not receive the full dose of Norvasc and, therefore, the study did not generate valid data supporting the product comparison.

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[1] Kario K, Pickering TF, Umeda Y, et al. Morning surge in blood pressure as a predictor of silent and clinical cerebrovascular disease in elderly hypertensives: a prospective study. *Circulation*. 2003;107:1401-1406.

[2] Lacourcière Y, Lenis J, Orchard R, et al. A comparison of the efficacies and duration of action of the angiotensin II receptor blocker telmisartan and amlodipine. *Blood Press Monit*. 1998;3:295-302.

The sales aid also includes a graphic that shows reductions in systolic and diastolic blood pressure for Micardis and Diovan based on ABPM, accompanied by the statement, "Delivers proven BP protection **vs Diovan (valsartan)** 80 mg and 160 mg – the most-prescribed angiotensin II receptor blocker (ARB)." Both the systolic (-11.0 mmHg Micardis vs. -8.7 mmHg Diovan, P=0.02 vs. Diovan) and diastolic (-7.6 mmHg Micardis vs. -5.8 mmHg Diovan, P=0.01 vs. Diovan) blood pressure reductions presented suggest that Micardis is superior to Diovan.

We are not aware of substantial evidence or substantial clinical experience demonstrating that Micardis is superior to Diovan. The reference provided for this claim does not provide substantial evidence or substantial clinical experience because the trial, among other design flaws, did not use the maximum labeled dose of Diovan (i.e., 320 mg daily). Furthermore, as a footnote in the sales aid points out, an identically designed European study did not substantiate a significant difference.

Omission of Risk Information

The sales aid fails to include risk information in each specific part as necessary to qualify the safety and effectiveness claims for Micardis and Micardis HCT.

One part of the sales aid, comprised of pages 2 and 3 promoting Micardis, presents the following effectiveness claims of blood pressure reduction with corresponding graphics presenting the changes in systolic and diastolic blood pressure at the end of the dosing period:

> Delivers proven BP reductions **vs Norvasc (amlodipine)** 5 mg and 10 mg—the most prescribed calcium channel blocker
>
> Delivers proven BP protections **vs Diovan (valsartan)** 80 mg and 160 mg—the most prescribed angiotensin II receptor blocker (ARB)

This part of the sales aid discloses information on the most common adverse events occurring with MICARDIS, but omits risk information regarding the use of Micardis in pregnancy, in patients with an activated renin-angiotensin system, in patients with impaired hepatic or renal function, and in patients with unilateral or bilateral renal artery stenosis.

Another part of the sales aid, page 4 promoting Micardis HCT, presents the following statements with graphics of the "Observed mean reduction from baseline in supine BP (mm Hg)":

> AFRICAN AMERICAN—The prevalence of hypertension in the African American population is among the highest in the world
>
> More than 2x the reduction in both SBP and DBP vs HCTZ alone

This part of the sales aid omits risk information regarding the use of Micardis HCT in pregnancy, hypersensitivity reactions, systemic lupus erythematosus, and lithium interactions. In addition, it omits risk information regarding patients with an activated renin-angiotensin system, and with unilateral or bilateral renal artery stenosis.

The pocket insert card, titled "REFERENCES," contains some risk information, but this is not sufficient to ensure that the claims in each part of the sales aid are truthful and non-misleading.

Conclusion and Requested Action

The sales aid contains unsubstantiated effectiveness and superiority claims and omits information on the risks associated with Micardis and Micardis HCT, and, therefore, misbrands the drugs in violation of section 502(a)of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. § 352(a).

DDMAC requests that Boehringer Ingelheim immediately cease the dissemination of promotional materials for Micardis or Micardis HCT the same as or similar to those described above. Please submit a written response to this letter on or before December 08, 2004, describing your intent to comply with this request, listing all promotional materials for Micardis or Micardis HCT the same as or similar to those described above, and explaining your plan for discontinuing use of such materials. Please direct your response to me at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm. 8B-45, 5600 Fishers Lane, Rockville, MD 20857, facsimile at (301) 594-6771. In all future correspondence regarding this matter, please refer to MACMIS #12589 in addition to the NDA numbers. We remind you that only written communications are considered official. If you choose to revise your promotional materials, DDMAC is willing to assist you with your revised materials by commenting on your revisions before you use them in promotion.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Micardis and Micardis HCT comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Lance McLeroy, Pharm.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

cc: Jane Wright-Mitchell, Pharm.D., J.D.
Abbott Laboratories

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Lance McLeroy

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