DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-162/S-005

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Pamela Cafiero, Ph.D.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Dear Dr. Cafiero,

Please refer to your supplemental new drug application dated December 18, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for MICARDIS HCT (telmisartan/hydrochlorothiazide) 40/12.5 mg and 80/12.5 mg Tablets.

We acknowledge receipt of your submission dated March 12, 2004.

This supplemental new drug application provides Chemistry, Manufacturing, and Control documentation and labeling to support a new 80/25 mg tablet strength. Draft labeling was submitted with the following revisions:

1. Under **DESCRIPTION**, 3rd paragraph, the first sentence that reads "Telmisartan is a white to off-white, odorless crystalline powder" has been changed to:

   Telmisartan is a white to slightly yellowish solid.

2. Under **DESCRIPTION**, the fifth paragraph has been changed to:

   MICARDIS HCT tablets are formulated for oral administration with a combination of 40 mg of telmisartan and 12.5 mg hydrochlorothiazide, or 80 mg of telmisartan and 12.5 mg or 25 mg hydrochlorothiazide. The tablets contain the following inactive ingredients: sodium hydroxide, meglumine, povidone, sorbitol, magnesium stearate, lactose monohydrate, microcrystalline cellulose, maize starch, sodium starch glycolate. As coloring agents, the 40 mg/12.5 mg and

80 mg/12.5 mg tablets contain iron oxide red, and the 80 mg/25 mg tablets contain iron oxide yellow. MICARDIS HCT tablets are hygroscopic and require protection from moisture.

3. Under **CLINICAL PHARMACOLOGY**, **Clinical Trials,** Telmisartan and Hydrochlorothiazide, the 2nd paragraph under this subheading has been changed to:

   The combination of telmisartan and hydrochlorothiazide resulted in additive placebo-adjusted decreases in systolic and diastolic blood pressure at trough of 16-21/9-11 mmHg for doses between 40/12.5 mg and 80/25 mg, compared to 9-13/7-8 mmHg for telmisartan 40 mg to 80 mg and 4/4 mmHg for hydrochlorothiazide 12.5 mg alone.

4. Under **PRECAUTIONS, Serum Electrolytes**, Telmisartan & Hydrochlorothiazide, the dosage strength of "80/25 mg" has been added to the first sentence of this subsection so that it now reads as follows:

   In controlled clinical trials using the telmisartan/hydrochlorothiazide combination treatment, no patient administered 40/12.5 mg, 80/12.5 mg or 80/25 mg had a decrease in potassium $\geq$ 1.4 mEq/L, and no patient experienced hyperkalemia. No discontinuations due to hypokalemia occurred during treatment with the telmisartan/hydrochlorothiazide combination. The absence of significant changes in serum potassium levels may be due to the opposing mechanisms of action of telmisartan and hydrochlorothiazide on potassium excretion on the kidney.

5. Under **PRECAUTIONS, Drug Interactions**, Telmisartan, *Other Drugs*, the drug "simvastatin" was added to the first sentence of this subsection. The first sentence now reads "Coadministration of telmisartan did not result in a clinically significant interaction with acetaminophen, amlodipine, glibenclamide, simvastatin, hydrochlorothiazide or ibuprofen."

6. Under **ADVERSE REACTIONS**, the last paragraph has been revised to:

   In controlled trials (n=1017), 0.3% of patients treated with MICARDIS HCT 40/12.5 mg, 80/12.5 mg or 80/25 mg discontinued due to orthostatic hypotension, and the incidence was 4%, 7%, and 1% respectively.

7. Under **ADVERSE REACTIONS**, **Telmisartan**, the following sentence has been added:

   In post-marketing experience, additional cases of angioedema and urticaria have been noted. (**Note:** urticaria was misspelled "urticariauticaria" in the draft labeling and should be corrected when the final printed labeling is submitted).

8. **Under DOSAGE AND ADMINISTRATION, Dose Titration by Clinical Effect**, this subsection has been revised to read as follows:

   MICARDIS HCT is available as tablets containing either telmisartan 40 mg and hydrochlorothiazide 12.5 mg, or telmisartan 80 mg and hydrochlorothiazide 12.5 mg or 25 mg. A patient whose blood pressure is not adequately controlled with telmisartan monotherapy 80 mg (see above) may be switched to MICARDIS HCT, telmisartan 80 mg/hydrochlorothiazide 12.5 mg once daily, and finally titrated up to 160/25 mg, if necessary.

   A patient whose blood pressure is inadequately controlled by 25 mg once daily of hydrochlorothiazide may be switched to MICARDIS HCT (telmisartan/hydrochlorothiazide 12.5 mg or telmisartan 80 mg/hydrochlorothiazide 25 mg) once daily. The clinical response to MICARDIS HCT should be subsequently evaluated and if blood pressure remains uncontrolled after 2-4 weeks of therapy, the dose may be titrated up to 160/25 mg, if necessary. Those patients controlled by 25 mg hydrochlorothiazide but who experiences hypokalemia with this regimen, may be switched to MICARDIS HCT (telmisartan 80 mg/hydrochlorothiazide 12.5 mg) once daily, reducing the dose of hydrochlorothiazide without reducing the overall expected antihypertensive response.

   (**Note:** the word "experiences" in the above paragraph should be changed to "experience" and should be corrected in the final printed labeling).

9. Under **HOW SUPPLIED**, the first paragraph has been revised and now reads as follows:

   MICARDIS HCT (telmisartan/hydrochlorothiazide) is available as bilayered, oblong-shaped, uncoated tablets, containing telmisartan 40 mg and hydrochlorothiazide 12.5 mg, or telmisartan

80 mg and hydrochlorothiazide 12.5 mg or 25 mg. The hydrochlorothiazide layer is red and unmarked for the 40/12.5 mg and 80/12.5 mg dose strengths, and yellow and unmarked for the 80/25 mg dose strength. The telmisartan layer is white to off-white, marked with the BOEHRINGER INGELHEIM logo and either H4 for the 40/12.5 mg dose strength, H8 for the 80/12.5 mg dose strength or H9 for the 80/25 mg dose strength. Tablets are provided as follows…

A new sentence has also been added after the packaging configurations for the 40/12.5 mg and 80 mg/12.5 mg that reads as follows:

MICARDIS HCT tablets 80 mg/25 mg are individually blister-sealed in cartons of 28 tablets as 4 x 7 cards (NDC 0597-0042-28).

10. The generic name "telmisartan/hydrochlorothiazide" has been inserted throughout the labeling after the brand name MICARDIS HCT.

We have completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the draft labeling (package insert included in your submission of December 18, 2003), revised as follows:

1. Under **DESCRIPTION**, change the first sentence of the fifth paragraph from:

   MICARDIS HCT tablets are formulated for oral administration with a combination of 40 mg of telmisartan and 12.5 mg hydrochlorothiazide, or 80 mg of telmisartan and 12.5 mg or 25 mg hydrochlorothiazide.

   To:

   MICARDIS HCT tablets are formulated for oral administration in three combinations of 40 mg/12.5 mg, 80 mg/12.5 mg and 80 mg/25 mg telmisartan and hydrochlorothiazide, respectively.

2. Under **How Supplied**, revise the first four sentences of the first paragraph to read as follows:

   MICARDIS HCT (telmisartan/hydrochlorothiazide) is available in three strengths as biconvex two-layered, oblong-shaped, uncoated tablets in three combinations of 40 mg/12.5 mg, 80 mg/12.5 mg and 80 mg/25 mg telmisartan and hydrochlorothiazide, respectively. The hydrochlorothiazide layer is red in the 40 mg/12.5 mg and 80 mg/12.5 mg tablets, and yellow in the 80 mg/25 mg tablets, and all are unmarked. The telmisartan layer for all three strengths is white, but may contain red specks in the 40 mg/12.5 mg and 80 mg/12.5 mg tablets and yellow specks in the 80 mg/25 mg tablets. The telmisartan layer is marked with the BOEHRINGER INGELHEIM logo and H4 for the 40 mg/12.5 mg dose strength, H8 for the 80 mg/12.5 mg dose strength and H9 for the 80 mg/25 mg dose strength.

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 21-162/S-005". Approval of this submission by FDA is not required before the labeling is used.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please contact:

Mr. Edward Fromm
Regulatory Health Project Manager
(301) 594-5332

Sincerely,

{See appended electronic signature page}

Douglas C. Throckmorton, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Doug Throckmorton

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