CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 21-162

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-162

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Ms. Heidi C. Reidies
900 Ridgebury Rd.
P.O. Box 368
Ridgefield, CT 06877-0368

Dear Ms. Reidies:

Please refer to your new drug application (NDA) dated December 29, 1999, received December 29, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Micardis HCT (telmisartan-hydrochlorothiazide) 40-12.5 and 80-12.5 mg Tablets.

We acknowledge receipt of your submission dated November 3, 2000 that constituted a complete response to our October 27, 2000 approvable letter.

This new drug application provides for the use of Micardis HCT (telmisartan-hydrochlorothiazide) 40-12.5 and 80-12.5 mg Tablets for the treatment of hypertension.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert and immediate container and carton labels included in your November 3, 2000 submission). Accordingly, the application is approved effective on the date of this letter.

Please make the following changes to the labeling at your next printing:

1) Under the **WARNINGS, Fetal/Neonatal Morbidity and Mortality** subsection, please delete the **Telmisartan & Hydrochlorothiazide in Animals, Telmisartan in Animals,** and **Hydrochlorothiazide in Animals** subheadings.

2) Under the **PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility** subsection, the second sentence of the second paragraph under the Hydrochlorothiazide subheading should be changed to:

   Positive test results were obtained in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays and in the *Aspergillus nidulans* non-disjunction assay.

We note that minor editorial changes have been made to the package insert.

Please change the second sentence of the **WARNINGS, Telmisartan in Animals** subsection of NDA 20-850, Micardis (telmisartan) Tablets to:

> In rabbits, embryolethality associated with maternal toxicity (reduced body weight gain and food consumption) was observed at 45 mg/kg/day [about 12 times the maximum recommended human dose (MRHD) of 80 mg on a mg/m^2 basis].

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not

to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We acknowledge your request of December 29, 1999 asking for a waiver of the pediatric study requirement for this action on this application. We agree to waive that requirement for this application for all pediatric age groups covered by the Pediatric Rule.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact: /S/

Edward Fromm
Regulatory Health Project Manager
(301) 594-5313

Sincerely,
/S/

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosed labeling Text

CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

OCT 27 2000

NDA 21-162

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Ms. Heidi C. Reidies
900 Ridgebury Rd.
P.O. Box 368
Ridgefield, CT 06877-0368

Dear Ms. Reidies:

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We acknowledge receipt of your submissions dated January 10, 14, and 18, February 15, and 22, March 22, April 26 and 27, May 5, 9, 12, and 24, June 19, July 14, 18, 27, and 28, August 4, 28, and 29, September 1, 8, 26, 27, and 29, and October 6, 2000.

This new drug application provides for the use of Micardis HCT (telmisartan-hydrochlorothiazide) 40-12.5 and 80-12.5 mg Tablets for the treatment of hypertension.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the enclosed marked-up draft labeling.

We remind you of your agreement to change the dissolution specification for both strengths of telmisartan/hydrochlorothiazide tablets to Q___ at ___ minutes for each of the tablet components, telmisartan and hydrochlorothiazide.

Please submit 20 paper copies of the final printed labeling ten of which are individually mounted on heavy weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999).

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, please contact:

Mr. Edward Fromm
Regulatory Health Project Manager
(301) 594-5313

Sincerely,

/S/

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Marked-up Draft Labeling

21 pages redacted from this section of the approval package consisted of draft labeling