CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 21-162

ADMINISTRATIVE DOCUMENTS

Required Information

(i)	Applicable Patent Numbers and Expiration Date of Each	U.S. Patent No. 5,591,762 January 7, 2014
(ii)	Type of Patent	drug, drug product and method of use
(iii)	Name of Patent Owner	Dr. Karl Thomae GmbH
(iv)	Entity authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 C.F.R §§ 314.52 and 314.95	Boehringer Ingelheim Pharmaceuticals, Inc.(the applicant), which has its place of business at 900 Ridgebury Road, PO Box 368, Ridgefield, CT 06877

Original Declaration with respect to a formulation, composition or method of use patent

The undersigned declares that Patent No. 5,591,762 covers the formulation, composition, and/or method of use of telmisartan/hydrochlorothiazide. This product is the subject of this application for which approval is being sought.

By: Alan Stempel

Alan Stempel

Capacity: ☐ Applicant's Agent (Representative)
☒ Applicant's Attorney

Date: December 13, 1999

EXCLUSIVITY SUMMARY FOR NDA # 21-162 SUPPL #_____

Trade Name MICARDIS HCT Generic Name telmisartan-hydrochlorothiazide

Applicant Name Boehringer Ingelheim HFD # 110

Approval Date If Known 11/17/00

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /✓/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /✓/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /✓/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

Form OGD-011347 Revised 10/13/98

cc: Original NDA Division File HFD-93 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /✓/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

NO

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO /✓/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /X/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-850 Telmisartan

NDA# 011-835 hydrochlorothiazide.

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /✓/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /✓/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /✓/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /✓/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study: 502.204 / 502.210, 502.214, 502.215, 502.216

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /✓/

Investigation #2 YES /___/ NO /✓/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /✓/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /✓/ ! NO /___/ Explain: _____

Investigation #2

IND # _____ YES /___/ ! NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

_____

/S/ 9/10/00

Signature Date

Title: CSO

/S/ 10/25/00

Signature of Office/ Division Director Date

cc: Original NDA Division File HFD-93 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at time of the last action.

NDA/BLA # 21-162 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8

HFD-110 Trade and generic names/dosage form: MICARDIS HCT (Telmisartan - hydrochlorothiazide) Tablets Action: AP AE NA

Applicant Boehringer Ingelheim Therapeutic Class 45

Indication(s) previously approved N/A

Pediatric information in labeling of approved indication(s) is adequate ___ inadequate ✓

Indication proposed in this application Treatment of hypertension

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ___Yes (Continue with questions) ___No (Sign and return the form)

IN WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

__Neonates (Birth-1month) __Infants (1month-2yrs) __Children (2-12yrs) __Adolecents(12-16yrs)

__1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

__2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

__3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

- __a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
- __b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
- __c. The applicant has committed to doing such studies as will be required.
  - __ (1) Studies are ongoing,
  - __ (2) Protocols were submitted and approved.
  - __ (3) Protocols were submitted and are under review.
  - __ (4) If no protocol has been submitted, attach memo describing status of discussions.
- __d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

✓ __4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

__5. **If none of the above apply,** attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE 4 COMMITMENTS IN THE ACTION LETTER? ___ Yes ✓ No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from DL Khatkowsky's (e.g., medical review, medical officer, team leader)

/S/ CSO 10/03/00

Signature of Preparer and Title Date

Orig NDA/BLA # 21-162
HF 110 /Div File
NDA/BLA Action Package
~~HFD-006/KRoberts~~

(revised 10/20/97)

FOR QUESTIONS ON COMPLETING THIS FORM, CONTACT KHYATI ROBERTS, HFD-6 (ROBERTSK)

HFD-104 (Crescenzi

Date: 10/03/00
To: NDA 21-162 telmisartan/Hydrochlorothiazide (T/H), for Hypertension
From: Abraham M. Karkowsky, M.D., Ph.D.
Subject: Grant for Full Pediatric Waiver

/S/

Boehringer Ingelheim Pharmaceuticals Inc, requested a full waiver for pediatric under 21CFR314.55(c)(2). Aside from this product, another AT1 blocker/hydrochlorothiazide combination product has been granted full pediatric waiver. The rationale for granting a waiver to T/H is similar to the other AT1/HCTZ product.

Two criteria need be established prior to granting a full pediatric waiver. That the drug product "not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients;"

The drug product, the T/H fixed dose combination is too inflexible to be useful in pediatric patients who are dosed on a mg/kg or mg/M^2 basis. The pediatric population that would potentially benefit by this fixed dose formulation is therefore small.

In addition, based on a NIH update of a 1987 task force report on hypertension in children and adolescents, children generally have secondary hypertension. The search and correction of the underlying process causing hypertension in these children is therefore, essential. For those needing control of blood pressure, diuretics and beta blockers have been historically used. ACE inhibitors, are currently the preferred treatment, except when the child has bilateral renal artery stenosis. Enalapril, currently has been granted an approvable recommendation for pediatric labeling. Since T/H would inhibit the same renin-angiotensin system, it is unlikely that this combination product would afford substantial additional benefit for pediatric populations. Other agents that have pediatric instructions or guidance for the treatment of hypertension include Aldomet, Chlorthiazide and Hydrochlorothiazide. While not an overwhelming pharmacopoeia for the treatment of hypertension, the addition of this combination product would not yield any significant benefit.

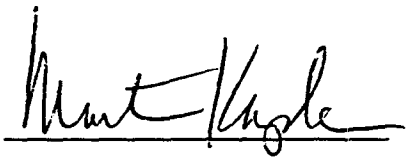
Since both aspects required by the current regulations have been fulfilled by T/H product, I recommend that the waiver be granted.

CC: Dr. Lipicky
Efromm.

CERTIFICATION REQUIREMENT

SECTION 306(k)(1) OF THE ACT
21 U.S.C. 355a(k)(1)

Boehringer Ingelheim Pharmaceuticals, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under subsection (a) or (b) [Section 306(a) or (b) of the Federal Food, Drug and Cosmetic Act in connection with Telmisartan/Hydrochlorothiazide Combination Tablets (40/12.5 mg and 80/12.5 mg).

Signature: 

Name of the Applicant: Martin Kaplan, M.D., J.D.
Vice President, Drug Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.

Date: December 14, 1999

Mailing Address: Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877-0368

Certification: Financial Interests and Arrangements of Clinical Investigators

In compliance with 21 CFR Parts 54.2 of the Food Drug and Cosmetics Act, Boehringer Ingelheim Pharmaceuticals Inc. hereby certifies that:

1. By company policy, no financial arrangements are ever made with investigators whereby the value of compensation is affected by clinical outcome

2. Boehringer Ingelheim Pharmaceuticals, Inc. is a privately held pharmaceutical company and none of the clinical investigators hold an equity interest in the company.

3. No clinical investigators have a proprietary interest in Telmisartan/Hydroclorothiazide Combination Tablets.

4. All controlled clinical studies provided in NDA 21-162, Original Application for Telmisartan/Hydrochlorothiazide Tablets application were completed prior to February 2, 1999. No significant payments, outside the costs of the clinical study, were made to investigators in the development of Telmisartan/Hydrochlorothiazide Combination Tablets.

Martin Kaplan, M.D., J.D.
Vice President, Drug Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.

12/14/99
Date

Telefax

Boehringer Ingelheim

Linda S. Carter
Food and Drug Administration HFD-101
Tel: 301-594-6758
Fax: 301-594-5298

Boehringer Ingelheim
Pharmaceuticals Inc.

July 21, 1999

Martin M. Kaplan, MD, JD
Telephone 203-798-4486
Telefax 203-791-6180
E-Mail
mkaplan@rdg.boehringer-ingelheim.com

900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368

Financial Disclosure Regulation

Dear Linda

Thank you very much for your helpful consultation yesterday concerning obligations by Boehringer Ingelheim Pharmaceuticals, Inc. to be in compliance with the recently implemented federal regulation on financial disclosure by clinical investigators on submission of the following two planned NDAs in 1999:

Telmisartan/hydrochlorothiazide tablets, 40/12.5 mg and 80/12.5 mg:
NDA 21-162 (current project manager: Natalia Morgenstern)

As we discussed, Boehringer Ingelheim is a family-owned, private company with no outside equity interests, stock, or stock options. By Company policy no financial arrangements are ever made with investigators where the value of compensation is affected by the clinical outcome of a study. Additionally, investigators do not have any proprietary interest in the study drug. The clinical trial studies in support of the were completed several years ago. The telmisartan/hydrochlorothiazide combination product NDA will be supported by two bioequivalence trials and studies previously provided to approved NDA 20-850 for MICARDIS® (telmisartan) tablets for adequate documentation of safety and efficacy.

It is our understanding that a signed certification by Boehringer Ingelheim incorporating the above statements would be sufficient for these two NDAs to be in compliance with the financial disclosure regulation.

We appreciate you communicating this agreement to the two reviewing divisions.

Sincerely,

Martin Kaplan

RHPM NDA Overview
October 25, 2000

NDA 21-162 Micardis HCT (telmisartan/hydrochlorothiazide) 40/12.5 and 80/12.5 mg Tablets

Sponsor: Boehringer Ingelheim Pharmaceuticals, Inc.

Classification: 4S

Date of Application: December 29, 1999
Date of Receipt: December 29, 1999
User Fee Goal Date: October 29, 2000

Background

Boehringer Ingelheim has submitted this NDA for the combination product telmisartan/HCTZ for the treatment of hypertension. Telmisartan monotherapy was approved for the treatment of hypertension under NDA 20-850 on November 10, 1998. Studies for the combination for the treatment of hypertension were performed under [redacted]

Meetings
February 11, 2000: Filing meeting.

September 28, 1994: End-of-Phase II meeting for telmisartan/hydrochlorothiazide.

Review

Medical
Medical Reviewer: Abraham Karkowsky, M.D., Ph.D.
Raymond Lipicky, M.D. (secondary review)

Labeling: see Dr. Karkowsky's 10-03-00 review for labeling recommendations.
Conclusion: Karkowsky: approvable
Lipicky: approvable

Statistical:
Reviewer: Lu Cui, Ph.D.
Labeling: None
Conclusion: Approvable

Biopharmaceutics:
Reviewer: Angelica Dorantes, Ph.D.
Labeling: None
Conclusion: approvable, but asked the sponsor to change the dissolution method and specifications for the 40/12.5 and 80/12.5 mg Tablets (see Dr. Dorantes' 9-15-00 review). The sponsor was notified by fax on September 15, 2000 of the Division's changes in dissolution method and specifications and agreed to them during a phone conversation with Dr. Marroum and Dr. Dorantes on September 27, 2000. A written confirmation of the agreement with the Division from the sponsor was

received by the Division on October 2, 2000 and is included in the Correspondence/Telecon/Faxes section of this action package.

Chemistry
Reviewer: Stuart Zimmerman, Ph.D.
Labeling: acceptable
cGMP Inspections: Acceptable, October 16, 2000
Methods validation: pending
Environmental Assessment: exclusion granted
Conclusion: approvable

Pharmacology
Reviewer: Gowra Jagadeesh, Ph.D.
Labeling: see Dr. Jagadeesh's June 13, 2000 review;

Conclusion: approvable

Statistics (preclin): Not needed

Safety Update: The sponsor provided additional safety information in a submission dated April 26, 2000.

Patent info: included in package

Pediatric info: waiver granted

DSI: Dr. Karkowsky said DSI audits were unnecessary.

Debarment Certification: included in package

OPDRA Tradename Review: The sponsors' proposed tradenames of and were found unacceptable by OPDRA on August 16, 2000. The firm then submitted the tradename, MICARDIS HCT which OPDRA found acceptable.

/S/

Edward J. Fromm

cc:
NDA 21-162
HFD-110
HFD-110/E.Fromm/Blount

AUG 16 2000

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: 5/12/00	**DUE DATE:** 7/15/00	**OPDRA CONSULT #:** 00-0154

TO:
Raymond Lipicky, M.D.
Director, Division of Cardio-Renal Drug Products
HFD-110

THROUGH: AUG 16 2000
Edward Fromm
Project Manager
HFD-110

PRODUCT NAME:	**MANUFACTURER:** Boehringer Ingelheim
(Telmisartan and Hydrochlorothiazide Tablets) 40 mg/12.5 mg and 80 mg/12.5 mg **NDA #:** 21-162	

SAFETY EVALUATOR: Peter Tam, R.Ph.

OPDRA RECOMMENDATION:

OPDRA does not recommend the use of the proprietary names.

/S/ for 8-16-00

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

/S/ 8/16/00

Peter Honig, M.D.
Director
Office of Post-Marketing Drug Risk Assessment
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: 8/3/00

NDA#: 21-162

NAME OF DRUG: ( )
(Telmisartan and Hydrochlorothiazide Tablets)
40 mg/12.5 mg and 80 mg/12.5 mg

NDA HOLDER: Boehringer Ingelheim

I. INTRODUCTION:

This consult is in response to a request from the Division of Cardio-Renal Drug Products, (HFD-110) on 5/12/00, to review the proposed proprietary name ( ) with regard to potential name conflict with existing proprietary/generic drug names.

PRODUCT INFORMATION

Telmisartan is currently marketed under the trade name, Micardis. The applicant wants to introduce a combination tablet that consists of telmisartan and hydrochlorothiazide called ( ).

( ) is a combination of telmisartan, an orally active, specific angiotensin II antagonist acting on the AT_1 receptor subtype, and hydrochlorothiazide, a diuretic.

Following oral administration, peak concentrations (C_{max}) of telmisartan are reached in 0.5-1 hour after dosing. Food slightly reduces the bioavailability of telmisartan, with a reduction in the area under the plasma concentration-time curve (AUC) of about 6% with the 40 mg tablet and about 20% after a 160 mg dose. The absolute bioavailability of telmisartan is dose dependent.

( ) is indicated for the treatment of hypertension. However, this fixed dose combination is not indicated for initial therapy. The usual starting dose of telmisartan is 40 mg once a day. Hydrochlorothiazide is effective in doses of 12.5 mg to 50 mg once daily. The combination is substituted for the titrated components.

( ) will be available in tablets containing 40 mg telmisartan and 12.5 mg hydrochlorothiazide and 80 mg telmisartan and 12.5 mg hydrochlorothiazide. The tablets are individually blister-sealed in cartons of 28 tablets as 4 x 7 cards.

II. RISK ASSESSMENT:

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[1,2,3] as well as several FDA databases[4] for existing drug names which sound alike or look alike to( )o a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[5]. An expert panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel Discussion was held by OPDRA to gather professional opinions on the safety of the proprietary names( ) Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed. This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1.( )

The suffix letter(")s too often confused with the number(" ")and might result in medication errors. The panel, therefore, considered this proposed name( )unacceptable.

2.( )

There were no proprietary names for currently marketed U.S. products identified by the Expert Panel that were believed to have significant look-alike and sound-alike properties. The panel was concerned that the suffix( )ould be interpreted as having some unique effectiveness . However, there are many proprietary names with the suffix( )hat are currently in the market. Examples are

---

[1] MICROMEDEX Healthcare Intranet Series, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Emergindex, Reprodisk, Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc).

[2] American Drug Index, online version, Facts and Comparisons, St. Louis, MO.

[3] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[4] Drug Product Reference File [DPR], the Established Evaluation System [EES], the AMF Decision Support System [DSS], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, and the electronic online version of the FDA Orange Book.

[5] WWW location http://www.uspto.gov/tmdb/index.html.

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Studies were conducted by OPDRA and involved 91 health professionals comprised of pharmacists, physicians, and nurses within FDA to determine the degree of confusion of with other drug names due to the similarity in handwriting and verbal pronunciation of the name. Inpatient and outpatient prescriptions were written, each consisting of (known/unknown) drug products and a prescription for (see below). These prescriptions were scanned into a computer and were then delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

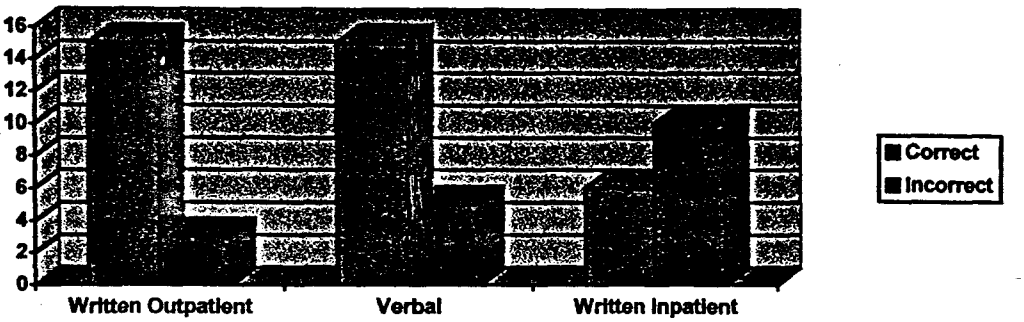
HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: Sig: One tablet by mouth every day	Sig: One tablet by mouth every day
Inpatient RX: Continue	

2. Results:

The results are summarized in Table I.

Table I

Study	# of Participants	# of Responses (%)	Correctly Interpreted	Incorrectly Interpreted
Written Outpatient	30	18(60%)	15	3
Verbal	30	20(67%)	16	4
Written Inpatient	31	16(52%)	6	10
Total	91	54(59%)	37(69%)	17(31%)



Thirty-one percent of the participants responded with the incorrect name. The incorrect written and verbal responses were summarized in Table II.

Table II

Written Outpatient	Incorrectly Interpreted
	*Micardis (2)
	Micardi
Verbal	Nycardis (4)
	*Micardice
Written Inpatient	Mirardis
	Muardis (2)
	Muardis
	*Micardis
	Miardis (2)
	Muardis 2)
	Meardis

* Existing Approved Product

C. SAFETY EVALUATOR RISK ASSESSMENT

The results of the verbal prescription study indicate that four (out of twenty) participants interpreted Micardis incorrectly. In the first written study (outpatient), three (out of eighteen) interpreted the name incorrectly. In the inpatient written study, ten (out of sixteen) participants interpreted the name incorrectly. This is possibly due to the poor handwritten prescription of the name. Many of the incorrect responses were misspelled/phonetic variations of the drug name. The incorrect interpretations in all three studies of the proposed name did overlap with one existing approved product, Micardis, which contains telmisartan alone. Two written respondents interpreted Micardis Micardis. One verbal respondent interpreted Micardi Micardice (similar spelling for Micardis in voice mail). A positive finding in a study with a small sample size may indicate a high risk and potential for medication errors.

D. STUDY SUBMITTED BY APPLICANT

The applicant, Boehringer Ingelheim, requested Brand Institute to evaluate the proposed proprietary name, Micardis for potential confusion with existing sound-alike and look-alike names. Brand Institute completed a four-phase study utilizing 50 physicians and 50 pharmacists to evaluate the proprietary name. The first phase involved physicians prescribing a verbal and written prescription to simulate actual prescribing processes. The second phase involved pharmacists who

interpreted the verbal and written prescriptions ordered by the physicians in phase one. This phase is unaided, i.e., the pharmacists are provided no information beyond the actual voice or handwritten recording of the name. Phase 3, which is also unaided, involved both physicians and pharmacists. Each was requested to identify similar brand/generic drug names and other safety issues based on various safety measurements. Phase 4 involved pharmacists only. Pharmacists were instructed to select the test drug name, which corresponds to the name they hear from the verbal prescription. In addition, pharmacists were instructed to select the drug name that corresponds to the name they read from a script graphic image. This phase is an aided study with positive and negative controls.

Results of phase 3 (physicians and pharmacists) demonstrated 30 of 80 respondents (38%), interpreted the modifier [redacted] as meaning "extra or extra strength". There was only 1 respondent (1%), who interpreted the modifier [redacted] a combination product.

Based on the above data, Brand Institute states that the results demonstrate the modifier [redacted] is an acceptable modifier since it clearly conveys that [redacted] communicates "extra or extra strength". However, this is misleading since Micardis [redacted] is actually a combination product consisting of telmisartan and hydrochlorothiazide.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels, carton and insert labeling of Micardis [redacted] OPDRA has attempted to focus on safety issues relating to possible medication errors. OPDRA has reviewed the current container labels and carton and insert labeling and has identified several areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENT

Post-marketing experience has demonstrated that similar packaging configurations for different drug products have contributed to medication errors. Therefore, the applicant should be encouraged to differentiate the product labeling of Micardis and Micardis [redacted]

B. UNIT DOSE CONTAINER LABEL

1. The blister packs are identical in appearance. We strongly recommend the product strengths be differentiated with the use of boxing, contrasting colors, or some other means.

2. There is limited room on the unit dose blister label. The inclusion of the days of the week crowds the label and appears unnecessary. OPDRA recommends the deletion of the days of the week to allow more room for the product name and strength.

3. We recommend the inclusion of the statement "Rx Only".

4. The established name should be revised to eliminate the backslash between "telmisartan and hydrochlorothiazide".

5. The dosage form (Tablets) should be included on all labels.

C. CARTON LABELING

1. The net quantity statement is confusing and could be simply stated as 28 tablets (4 x 7 tablet blister cards).

2. The "Each tablet contains ...." statement should be relocated so it does not appear in conjunction with the net quantity.

3. The "manufacturer/distributor" statement should be revised to delete the statement "licensed from Boehringer Ingelheim....." [see 21 CFR 201.1 (g)(5)].

4. A statement should be included as to whether or not the unit dose package is child resistant. If it is not child-resistant, we encourage the inclusion of a statement (see below) that if dispensed for outpatient use, a child resistant container should be utilized.

   "This unit-dose package is not child-resistant. If dispensed for outpatient use, a child resistant container should be utilized".

5. The "Usual Dosage" statement should be revised to read as follows:

   Usual Dosage: One tablet daily.

D. INSERT LABELING

Micardis is not indicated for initial therapy. However, this message is not conveyed until the third paragraph of this section. A practitioner may interpret the directions "the usual starting dose of telmisartan is 40 mg once daily" as beginning a once daily dose of the 40 mg/12.5 mg combination product. OPDRA recommends inserting "Micardis is not recommended for initial therapy" as the first sentence of paragraph one.

APPEARS THIS WAY
ON ORIGINAL

IV. RECOMMENDATIONS:

1. OPDRA does not recommend the use of the proprietary names, Micardis and Micardis

2. OPDRA recommends the above labeling revisions that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

OPDRA would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Peter Tam at 301-827-3241.

/S/

Peter Tam, R.Ph.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

/S/ for 8-16-10

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

Electronic Mail Message

Date: 9/8/00 3:18:17 PM
From: Jerry Phillips (PHILLIPSJ)
To: Edward Fromm (FROMME)
Cc: Sammie Beam (BEAMS)
Subject: MICARDIS HCT

Hi:

OPDRA has reviewed the proposed proprietary name MICARDIS HCT for NDA 21-162 in response to your 8/3/00 consult. Since Micardis is already an approved product, the modifier HCT is acceptable for this combination product of telmisartan and hydrochlorothiazide. Thus, OPDRA has no objection to the approval of the proprietaty name MICARDIS HCT. If you have any further questions, please feel free to contact me. Thanks.

Jerry Phillips
Associate Director, OPDRA