CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 20-727

Administrative/Correspondence Reviews

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
20-727

NAME OF APPLICANT / NDA HOLDER
NitroMed Inc

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
BiDil®

ACTIVE INGREDIENT(S)	STRENGTH(S)
Isosorbide Dinitrate	20 mg Isosorbide Dinitrate
Hydralazine hydrochloride	37.5 mg Hydralazine hydrochloride

DOSAGE FORM
Tablet

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

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r each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the ..nformation described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
U.S. 6,784,177 B2	8/31/2004	9/8/2020

d. Name of Patent Owner
NitroMed Inc.

Address *(of Patent Owner)*
125 Spring Street

City/State
Lexington, MA

ZIP Code	FAX Number *(if available)*
02421	781-274-8080
Telephone Number	**E-Mail Address *(if available)***
781-266-4000	

e. Name of agent or representative who resides or maintains a place of business within the United States 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 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address *(of agent or representative named in 1.e.)*

City/State

ZIP Code	FAX Number *(if available)*
Telephone Number	**E-Mail Address *(if available)***

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

004

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.

Not applicable

2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

Drug Product (Composition/Formulation)

	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No

4.2 Patent Claim Number *(as listed in the patent)*: see 4.2a

Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No

4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.

Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*

Since original proposed labeling was submitted in 1996 and found not approvable, an additional efficacy trial including numerous clinical endpoints was undertaken. Labeling resulting from this trial will be submitted in an upcoming filing. Therefore, no proposed labeling is currently available to reference.

5. No Relevant Patents

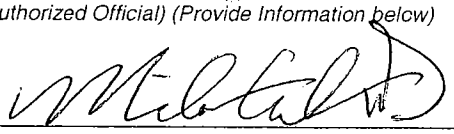
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in manufacture, use, or sale of the drug product. ☐ Yes

005

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	12/9/04

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name NitroMed Inc.	
Address 125 Spring Street	City/State Lexington , MA
ZIP Code 02421	Telephone Number 781-266-4000
FAX Number *(if available)* 781-274-8080	E-Mail Address *(if available)*

006

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

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TRADE NAME (OR PROPOSED TRADE NAME)
BiDil®

ACTIVE INGREDIENT(S)	STRENGTH(S)
Isosorbide Dinitrate Hydralazine hydrochloride	20 mg Isosorbide Dinitrate 37.5 mg Hydralazine hydrochloride

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r each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
U.S. 4,868,179	9/19/1989	4/22/2007

d. Name of Patent Owner
NitroMed Inc.

Address *(of Patent Owner)*
125 Spring Street

City/State
Lexington, MA

ZIP Code	FAX Number *(if available)*
02421	781-274-8080
Telephone Number	**E-Mail Address *(if available)***
781-266-4000	

e. Name of agent or representative who resides or maintains a place of business within the United States 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 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address *(of agent or representative named in 1.e.)*

City/State

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f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☒ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

007

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? ☐ Yes ☒ No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? ☐ Yes ☒ No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). ☐ Yes ☐ No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

Not applicable

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) ☐ Yes ☒ No

2.6 Does the patent claim only an intermediate? ☐ Yes ☒ No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) ☐ Yes ☐ No

Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? ☐ Yes ☒ No

3.2 Does the patent claim only an intermediate? ☐ Yes ☒ No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) ☐ Yes ☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No

4.2 Patent Claim Number *(as listed in the patent)*

see 4.2a

Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.

Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*

Since original proposed labeling was submitted in 1996 and found not approvable, an additional efficacy trial including numerous clinical endpoints was undertaken. Labeling resulting from this trial will be submitted in an upcoming filing. Therefore, no proposed labeling is currently available to reference.

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008

6. Declaration Certification

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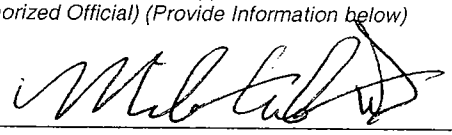	12/9/04

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009

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U.S. 6,465,463 B1	10/15/2002	9/8/2020

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City/State
Lexington, MA

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f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

010

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2. Drug Substance (Active Ingredient)

Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? ☐ Yes ☒ No

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2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). ☐ Yes ☐ No

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Not applicable

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) ☐ Yes ☒ No

2.6 Does the patent claim only an intermediate? ☐ Yes ☒ No

2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) ☐ Yes ☐ No

Drug Product (Composition/Formulation)

Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? ☐ Yes ☒ No

3.2 Does the patent claim only an intermediate? ☐ Yes ☒ No

3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) ☐ Yes ☐ No

4. Method of Use

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4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No

4.2 Patent Claim Number *(as listed in the patent)*

see 4.2a

Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No

4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.

Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*

Since original proposed labeling was submitted in 1996 and found not approvable, an additional efficacy trial including numerous clinical endpoints was undertaken. Labeling resulting from this trial will be submitted in an upcoming filing. Therefore, no proposed labeling is currently available to reference.

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011

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6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	12/9/04

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

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Name NitroMed Inc.	
Address 125 Spring Street	City/State Lexington , MA
ZIP Code 02421	Telephone Number 781-266-4000
FAX Number *(if available)* 781-274-8080	E-Mail Address *(if available)*

012

MEDCO RESEARCH, INC.

DUPLICATE

PATENT CERTIFICATION

September 12, 1996

Raymond J. Lipicky, M.D.
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products
Attention: Document Control Room, HFD-110
5600 Fishers Lane
Rockville, Maryland 20857

NEW CORRESP
XR

RE: NDA 20-727
BiDil®(hydralazine hydrochloride and isosorbide dinitrate) Tablets

Dear Dr. Lipicky:

Reference is made to a telephone call received from Mr. Gary Buehler, of FDA, on July 12, 1996, concerning our New Drug Application for BiDil Tablets submitted on July 3, 1996.

As requested by Mr. Buehler, information pertaining to patent certifications for BiDil Tablets and the two drug substances used, hydralazine hydrochloride and isosorbide dinitrate, are attached. As a result of the search performed, only two patents were found relating to isosorbide dinitrate. Copies of these patents are provided herein.

We certify that the information covered in these two patents are not claims for which approval is being sought in our New Drug Application 20-727 for BiDil Tablets.

Should you require any additional information, please do not hesitate to contact me at 919-549-8117.

Sincerely,

Anne McKay

Anne McKay
Director, Regulatory Affairs

DUPLICATE

P.O. BOX 13886 • RESEARCH TRIANGLE PARK, NC 27709 • PHONE: (919) 549-8117 • FAX: (919) 549-7515

BiDil®(hydralazine hydrochloride and isosorbide dinitrate) Tablets

NDA 20-727

AMENDMENT

The following data are provided in response to an FDA telephone request of July 12, 1996.

Table of Contents

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WILLIAM G. TODD
IRA B. WINKLER
JAMES M. BOLLINGER
PORTER F. FLEMING
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JEFFREY A. HOVDEN
ADAM T. BERNSTEIN
R. THOMAS PAYNE*

MICHAEL EBERT
OF COUNSEL

*NOT ADMITTED IN NEW YORK

VIA FEDERAL EXPRESS

August 1, 1996

Ms. Anne McKay
Director
Drug Regulatory Affairs
Medco Research, Inc.
P.O. BOX 13886
Research Triangle Park, NC 27709

Re: FDA/NDA patent information
Our Reference: 1541-000

Dear Anne:

The following is in response to your request for additional patent information on the Bidil® tablets.

Bidil®

1. U.S. Patent No. 4,868,179

I. Expiration date: April 22, 2007

II. Type of patent: Method of using a combination of hydralazine and isosorbide dinitrate

III. Patent owner: Jay N. Cohn

IV. U.S. Patent No. 4,868,179 covers the method of using Bidil® tablets for congestive heart failure.

2. U.S. Patent No. 4,156,736

   I. Expiration date: May 19, 1997

   II. Type of patent: Method of making an aqueous isosorbide dinitrate solution

   III. Patent owner: Sanol Schwarz-Monheim GmbH

   IV. U.S. Patent No. 4,156,736 does <u>not</u> cover a therapeutic combination of hydralazine and isosorbide dinitrate.

3. U.S. Patent No. 4,584,315

   I. Expiration date: April 22, 1990 (for failure to pay Patent Office maintenance fee)

   II. Type of patent: Method of using nitroglycerin or isosorbide dinitrate in combination with hydralazine or diazoxide or minoxidil or sodium nitroprusside

   III. Patent owner: Upjohn Company

   IV. U.S. Patent No. 4,584,315 did <u>not</u> cover a therapeutic method for congestive heart failure.

Please call us with any further inquires you may have.

Very truly yours,

Jae H. Kim

cc: Jeffrey L. Hill

United States Patent [19]

Marshall

[11] Patent Number: 4,584,315

[45] Date of Patent: Apr. 22, 1986

[54] METHOD OF TREATING ISCHEMIC STATES

[75] Inventor: Norman B. Marshall, Portage, Mich.

[73] Assignee: The Upjohn Company, Kalamazoo, Mich.

[21] Appl. No.: 561,013

[22] Filed: Dec. 13, 1983

Related U.S. Application Data

[62] Division of Ser. No. 321,367, Nov. 16, 1981, abandoned.

[51] Int. Cl.[4] A61K 31/35; A61K 31/215

[52] U.S. Cl. 514/456; 514/507; 514/929

[58] Field of Search 424/283, 298; 514/456, 514/507, 929

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[57] ABSTRACT

The present invention relates to novel methods of use for known pharmacological anti-allergenic agents including disodiumchromoglycate (DSCG) and related compounds thereof, including generally bis chromones, benzopyrans, oxamic acids and salts or esters of each, preferably lodoxamide, its THAM salt and ethyl ester. All are subsequently included in the term biologues. The methods are for the treatment of pathological cardiovascular ischemic states in animals, particularly humans. Additionally, novel compositions incuding the biologues of the present invention in combination with known vasodilators and feed stuffs are also disclosed.

2 Claims, No Drawings

METHOD OF TREATING ISCHEMIC STATES

This application is a divisional application of application Ser. No. 321,367, filed Nov. 16, 1981, now abandoned.

BACKGROUND OF THE INVENTION

The present invention relates to novel methods of using known pharmacological agents in man. The invention further relates to novel compositions employing these known pharmacological agents for the treatment of various conditions or diseases in animals. Particularly, the present invention relates to the use of these known pharmacological agents in the treatment of pathological cardiovascular ischemic states (PACVIS) in animals and man.

The cardiovascular ischemic states whose treatment comprises the subject matter of the present invention are those states arising from physiological processes, particularly frankly pathological processes in which necrosis develops in smooth or striated muscles or skin.

The cardiovascular ischemic state, which leads to the development of necrosis in the cardiac muscle, includes, for example, angina, vasospastic angina, the sudden death syndrome, and the like. The ischemia resulting from these states is well known and is readily diagnosed by an attending physical or veterinarian.

The cardiovascular ischemic states directly involving necrosis of smooth or striated muscle or skin include a wide variety of diseases and conditions. Further, certain cardiovascular ischemic states are a recognized untoward consequence of numerous other diseases and conditions.

One principle class of cardiovascular ischemic states is a consequence of the various forms or types of vasospasms. Vasospasms refers to the abnormal spasm of the blood vessels, resulting in decrease in their caliber. Ischemic in this invention refers to the condition of having local and temporary deficiency of blood, due to the contraction of a blood vessel.

Although it is known that the pharmacological agents now found to be useful in the treatment of pathological cardiovascular ischemic states were previously known for use as anti-allergenic agents, the mechanism for such previously known use is not appreciated. It is known that histamine plays a role in allergic reactions. Further this amine is a potent, easily released and functional endogenous compound in the body. For example, mast cells are the cells having granules in which histamine is highly concentrated. Histamine acts on two separate and distinct receptors, termed H_1 and H_2 receptors. Both H_1 and H_2 receptors mediate the vasodilator effects of histamine. Thus, the mast cells function in the healthy vertebrate by the release of histamine. However, the specific influences of the mast cell on ischemia is not well understood. For this reason, advantages of the present invention patentably extend methods of treating pathological cardiovascular ischemic states (PACVIS). See Goth et al., "Histamine", *Medical Pharmacology*, chap. 15, pp. 177-188, 9th ed., C. V. Mosby Co., St. Louis, (1978).

Vasospasm is a condition common in adults and typically results in a deficiency of blood to muscle or skin which is then at risk of developing necrosis. Vasospasms typically result in numerous systematic manifestations, characterized by ischemic disorders. Various types of vasospasms associated with ischemia are known. See for example, *The Merck Manual*, 13th edition, Merck, Sharp and Dohme Research Laboratories, Rahway, N.J. (1977). Among the types of vasospasms are those which produce angina pectoris attributed to myocardial ischemia. These vasospasms may progress to myocardial infarction, attributable to ischemic myocardial necrosis following an abrupt reduction in coronary flow to a segment of the myocardium. Vascular spasm may also contribute to occlusion of the abdominal aorta and its branches, such as splanchnic artery occlusion, renal artery occlusion, or occlusion at the bifurcation, and peripheral vascular disorders consequent to occlusive arterial diseases. Other notable disease states whose principle long term pathology arises from vasospasms as a constituent thereof include functional peripheral arterial disorders, such as Reynaud's phenomenon, acrocyanosis, and, rarely, erythromalagia. For example, Reynaud's disease may be idiopathic or secondary to such conditions as occlusive arterial disease. Likewise, such pathology may result from connective tissue disorders; such as, progressive systemic sclerosis, neurogenic lesions, drug intoxication, dysproteinemias, myxedema, primary pulmonary hypertension, and trauma. Much less severe in its ultimate effect is the cardiovascular ischemic state resulting from acrocyanosis.

Other disease conditions also induce pathological cardiovascular ischemic states (PACVIS) with resulting untoward effects on the affected animal. For example, arterial embolism or thrombosis may be due to a number of causes in an animal having a history of ischemia associated with vasospasms. Further, in many peripheral vascular diseases the vasospastic disorders induce pathological cardiovascular ischemic states with resulting pathological consequences.

Other vasospastic diseases also have the effect of inducing a pathological cardiovascular ischemic state, for example, immersion foot, trench foot, herpes zoster, decubitous ulcers, and diabetic gangrene.

Finally, while many cardiovascular ischemic states have been attributed in the past to excess vasospasm, measuring the extent of ischemia is a more recent development. Consequently, limiting the extent of the ischemia has likewise been difficult. For example, it has long been known in myocardial infarction that cardiac peformance after recovery depends essentially on the mass of functioning muscle surviving the acute episode. Reinfarction or extension of infarct during hospitalization is common. The use of increased inspired O_2 concentration is one avenue of treatment. Recent animal studies suggest that reduction of the O_2 requirements of myocardium and an increase in coronary perfusion or reduction of after load with vasodilators reduce the area of ischemic infarction. The primary effects may be based on the lowering of peripheral resistance. These observations need further evaluation but in selected patients, especially those with elevated pressures, it appears to be appropriate in the acute stages of infarction to use vasodilators. These include such known agents as nitroglycerin, isosorbide dinitrate, trimethafan, or nitroprusside.

Measuring the ischemic myocardium at risk of necrosis is discussed by DeBoer et al. in "Autoradiographic Method for Measuring the Ischemic Myocardium at Risk: Effects of Verapamil on Infarct size after Experimental Coronary Artery Occlusion", *Proc. Natl. Acad. Sci.* U.S.A., vol. 77, no. 10, pp. 6119-6123, October, 1980, Medical Sciences. Such measurement in the inves-

tigation of pharmacological agents is advantageous since myocardial infarct size appears to be a function of ischemia myocardium at risk of developing necrosis. Numerous methods have been reported for assessing the effectiveness of pharmacological agents including by indirect methods. For example, one such report indicates determination of epicardial enosis. See Kloner, R A. et al., *Circulation*, vol. 58, pp. 220–226 (1978). Another indirect method is described as "Factors Influencing Infarct Size Following Experimental Coronary Artery Occlusions" by Maroko, P. R. et al., *Circulation*, vol. 43, pp. 67–82 (January, 1971). Direct methods include postmortem injection of dyes described by Reimer, K. A. et al. *Lab. Invest.*, vol. 40, pp. 633–644 (1979) or angiographic contrast agents described by Jugdutt, B. I. et al., *Circulation*, vol. 60, pp. 1141–1150 (1979), Jugdutt, B. I. et al., *Circulation*, vol. 59, pp. 734–743 (1979), Hoffman, M. et al. *Circulation*, vol. 60, II-215A (ABSTR.) (1979).

An efficient means of assessing the inhibition of cardiovascular ischemic states by a chemical agent is described by DeBoer et al., cited above. The method of DeBoer et al. determines the ability of a chemical agent to affect infarct size. The first objective of this study is to determine the physiological status of coronary blood flood after the coronary arterial occlusion but prior to the administration of drugs. The second objective of this study is to use autoradioagraphy to test the efficacy of delayed administration of the drug, in this case verapamil, in reducing myocardiam infarction size

The technique of DeBoer et al. for measuring the reduction of myocardial infarct size employs the techniques described in the above noted DeBoer et al. article. Thirty minutes after left anterior decending coronary occlusion mongrel dogs are randomized into control or treatment groups. Ischemic bed size (area at risk) is determined both before treatment by the injection of 99m Tc labeled albumin microspheres with postmortem autoradioagraphy (AR-R) and during treatment by left atrial dye injection immediately before sacrifice (AR-D). Infarct size (IS) is determined six hours after coronary arterial occlusion by triphenyl tetrazolium staining and expressed as percent of left ventrical before occlusion.

In summary, the compounds of this invention are substituted in the DeBoer et al. techniques. By measuring their inhibition of the ischemic state, it is understood that the spread of necrosis is likewise inhibited which consequently reduces the size of the infarction following a coronary occlusion.

It is by this method that the efficacy of the known compounds are evaluated for the instant invention.

The known compounds employed in the novel methods and compositions disclosed herein are previously known as anti-allergenic agents specifically including disodiumchromoglycate (DSCG) and DSCG anti-allergenic biologues. Hereinafter DSCG and DSCG anti-allergenic biologues are referred to in the invention by the term "biologues." These biologues include anti-allergenic bis chromones related to DSCG. Both DSCG and bis chromones related to DSCG are described in U.S. Pat. No. 3,419,578. Further related anti-allergenic bis chromones are those described in U.S. Pat. Nos. 3,519,652 and 3,673,218. Moreover, additional compounds of the invention biologues, including anti-allergenic uses therefore, are described in U.S. Pat. No. 4,046,910, issued Sept. 6, 1977. The description of DSCG and related anti-allergenic bis chromones which are the biologues of the present invention and their anti-allergenic compositions are incorporated here by reference from U.S. Pat. Nos. 3,419,578, 3,519,652, 3,673,218, and 4,046,910.

Another class of compounds within the biologues of the present invention are the anti-allergenic benzopyrans, particularly the compounds described in U.S. Pat. Nos. 4,159,273, 3,786,071, 3,952,104, and 4,055,654. Notable among these compounds is proxicromil (FPL 57,787), 6,7,8,9-tetrahydro-5'-hydroxy-4-oxo-10-propyl-4H-naphtho[2,3-b]pyran-2—carboxylic acid, described in Example 8 of U S. Pat. No. 4,159,273. The description and anti-allergenic compositions of these anti-allergenic benzopyrans are incorporated here by reference from U.S. Pat. Nos. 4,159,273, 3,786,071, 4,055,654, and 3,952,104.

Yet, another class of compounds within the biologues of the present invention are the anti-allergenic oxamic acids or derivatives thereof. These compounds, together with their anti-allergenic uses and compositions, are described in U.S. Pat. Nos. 3,993,679, 4,159,278, 4,095,028, 4,089,973, 4,011,337, 4,091,011, 3,972,911, 4,067,995, 3,980,660, 4,044,148, 3,982,006, 4,061,791, 4,017,538, 4,119,783, 4,113,880, 4,128,660, 4,150,140, 3,966,965, 3,963,660, 4,038,398, 3,987,192, 3,852,324, and 3,836,541. The preparations of such compounds and their anti-allergenic compositions are incorporated by reference here from the aforementioned United States patents. The most preferred biologue in the present invention is the dioxamate N,N'-(2-chloro-5-cyano-m-phenylene)dioxamic acid (lodoxamide). Among lodoxamides preferred forms are the bis THAM, (tris(hydroxymethyl)-amine methane) salt and the diethyl ester, particularly the diethyl ester.

PRIOR ART

DSCG and its anti-allergenic biologues and anti-allergenic uses, therefore, are known in the art. See the various United States patents cited above. Additionally, see copending U.S. application Ser. No 168,827, filed July 10, 1980, which is a continuation-in-part of Ser. No. 073,394, filed Sept. 7, 1979 and Ser. No. 073,400, filed Sept. 7, 1979, for disclosure of further utility as agents for the treatment of pathological mineral resorptive states of the DSCG and anti-allergenic biologues of this invention. Further known are numerous vasodilating agents. See Goth et al., *Medical Pharmacology*, "Coronary Vasodilators", 9th ed., pp. 408–413, The C. V. Mosby Company, St. Louis, Mo. (1978), for examples of such agents.

With respect to DSCG, this agent has been reported to inhibit mast cell degranulation of monkey gingiva. See Nuki, K. et al., "The Inhibition of Mast Cell Degranulation In Monkey Gingiva by Disodium Cromoglycate", *J. Periodontal. Res.* 10:282–287 (1975) and references cited therein. Two references of particular interest cited therein are Goldhaber, P., "Heparin Enhancement of Factors Stimulating Bone Resorption in Tissue Culture", *Science* 147:407–408 (1965), and Shapiro, S. et al., "Mast Cell Population in Gingiva Affected by Chronic Destructive Periodontal Disease", *Periodontics* 40:276–278 (1969).

SUMMARY OF THE INVENTION

The present invention particularly provides:

(1) A method of arresting or preventing a pathological cardiovascular ischemic state (PACVIS) in an ani-

mal exhibiting or susceptible to the development of said PACVIS which comprises:

systemically administering to said animal an amount of an anti-PACVIS biologue effective to treat or prevent said PACVIS;

(2) In a method of preventing or treating a pathological cardiovascular ischemic state (PACVIS) with one or more known vasodilating agents comprising coronary vasodilators such as nitroglycerin, isosorbide dinitrate, or direct vasodilators such as trimethafan or nitroprusside, the improvement which comprises:

concomitantly administering an amount of an anti-PACVIS biologue which together with said known vasodilator agent or agents is effective to prevent or arrest said PACVIS;

(3) In a unit dose of a pharmaceutical composition for preventing or treating a pathological cardiovascular ischemic state (PACVIS) with one or more known coronary or direct vasodilating agents comprising nitroglycerin, isosorbide dinitrate, trimethafan, or nitroprusside, the improvement which comprises:

an amount of anti-PACVIS biologue which together with said known vasodilating agent or agents is an effective unit dose to prevent or arrest said PACVIS;

(4) an animal feed for feeding to an animal suffering from or susceptible to the development of a pathological cardiovascular ischemic state (PACVIS) which comprises:

an anti-PACVIS biologue in a concentration such that an amount thereof which will be injested by the animal over a predetermined interval contains an amount of said anti-PACVIS biologue effective to arrest or prevent said PACVIS during said predetermined interval;

(5) A feed premix for preparing an animal feed for feeding to an animal suffering from or susceptible to the development of a pathological cardiovascular ischemic state (PACVIS) which comprises:

an anti-PACVIS biologue in a concentration such that when said animal feed premix is diluted with animal feed an amount thereof which will be injested in a predetermined interval contains an amount of said anti-PACVIS biologue effective to arrest or prevent said PACVIS during said predetermined interval.

The methods or compositions of the present invention is especially preferred to treat humans for limiting infarct size following a coronary occlusion.

The present invention relates to the treatment of animals, although mammals represent particularly preferred embodiments of the present invention. Most preferred is the treatment of humans by the instant method. The present invention thus provides a method of treating both humans and valuable domestic mammals such as bovine, equine, canine, and feline species, and chickens, turkeys, geese, ducks, and other fowl.

The present invention relates to the arrest or prophylaxis of pathological cardiovascular ischemic states or of "PACVIS". The employment of sound medical therapy requires that the anti-PACVIS agent be employed prophylactically only in cases where the animal or patient is particularly susceptible to the development of PACVIS. The conditions and circumstances which increase susceptibility are readily ascertained to the ordinarily skilled physician or veterinarian and include:

(1) Coronary vasospasm which includes angina pectoris, vasospasmic angina, myocardial infarction;

(2) Peripheral vasospasm in peripheral vascular diseases which includes Reynaud's phenomen, mesenteric ischemia, "hepatorenal syndrome";

(3) Cerebral vasospasm;

(4) A diagnosis of any disease or condition in which a PACVIS is a potential consequence such as from arrhythmic diseases.

In the prophylactic use of these anti-PACVIS agents, the dose effective for the prevention of the PACVIS is determined by patient or animal response, as discussed hereinafter for therapeutic uses, and is, in general, somewhat less than the dose required to treat a PACVIS.

A PACVIS which is arrested or prevented in accordance with the present invention includes each of the various states or conditions described above where the long-term effects on the animal are untoward, and hence the condition or state is associated with a direct or indirect pathological process.

A PACVIS is not an uncommon condition encountered in medical or veterinary practice. Accordingly, the diagnosis of a PACVIS is readily undertaken by the ordinarily skilled physician or veterinarian.

The dose regimen for the anti-PACVIS biologue employed is selected in accordance with a variety of factors, including the type, age, weight, sex, and medical condition of the mammal, the severity of PACVIS and its duration, and the particular anti-PACVIS biologue being administered. An ordinarily skilled physician or veterinarian, subsequent to the diagnosis of a PACVIS, will readily determine and describe the effective amount of the anti-PACVIS biologue to arrest the progress of the condition. In so proceeding, the physician or veterinarian would, for example, employ relatively low dosages of the anti-PACVIS biologue, subsequently increasing dose until a maximum response was obtained. Such a response is obtained when the ischemia begins to decrease and subsequently substantially ceases, or at a minimum remains much reduced.

The anti-PACVIS biologues are the various anti-allergenic agents known in the art as discussed above. Such substances include DSCG, other anti-allergenic bis chromones, anti-allergenic benzopyrans and preferably anti-allergenic oxamic acids or derivatives (oxamates).

Various formulations may be employed including nasal drops, oral hard filled capsules, nebulized aerosols, interdermal patches, or intravenous dosages. Routes of administration include oral, insufflation, intranasal, intrabronchial, subcutaneous and intravenous; oral and insufflation being preferred.

When DSCG is employed as the anti-PACVIS biologue the compound is most preferably administered either intranasally or by insufflation. The dosage may be 5-400 mg per patient per dose but preferably is about 20 mg. Dosages administered through the nasal route are by sterile solution of from ½ percent to 10 percent concentration with approximately 2 percent concentration preferred. Equivalent parental or oral dosages can also be administered. When dosages significantly higher than 20 mg per patient particularly by insufflation are employed, the systemic toxicity of DSCG must be carefully evaluated and subsequent dosages determined by evaluating the benefit of the drug in relation to any such toxic manifestations.

For anti-PACVIS bis chromones routes of administration which may be employed include intranasal, insufflation, oral, interdermal or as an injectable both intramuscular and intravenous. Effective dosage equiv-

alent to the DSCG dose above may be determined and employed as described above. Initial dosages of anti-PACVIS oxamate or benzopyran may be determined by administering minimum dosages and subsequently evaluating increasing dosages determined by the benefit of the drug in relation to toxic manifestations thereof.

The preferred oxamate, lodoxamide, described above provides a particularly efficacious result when administered rectally, intranasally, by insufflation, orally, intradermally or as an injectable. The dosage range for insufflation (aerosol), rectal, intranasal or intradermal administration is from 0.0001 mg/dose to 20 mg/dose. These routes of administration have a preferred dosage range of from 0.01 mg/dose to 10 mg/dose. Oral dosage ranges for the preferred THAM salt of lodoxamide is from 0.1 mg/dose to 100 mg/dose. The diethyl ester of lodoxamide is preferably administered by the oral route at a dosage range of from 0.5 mg/dose to 30 mg/dose. Finally, the dosage range for injectable oxamates is from 0.0001 mg/dose to 5 mg/dose, preferably 0.001 mg/dose to 1 mg/dose. When dosages of above 5 mg per patient per dose orally are employed, the systemic toxicity of the anti-PACVIS oxamate or benzopyran must be carefully evaluated and subsequent dosages determined by evaluating the benefit of the biologue in relation to any such toxic manifestations.

In order to obtain the efficacious result provided by the present invention, a route of administration permitting systemic action may be required, as indicated above. Where localized effects are exerted by absorption, topical applications may be especially preferred. Thus, in the treatment of a PACVIS secondary to myocardial infarction, liquids or gels or viscous fluids may be preferred vehicles when applied to the appropriate localized chest area.

Generally, for anti-PACVIS biologues known to be orally active the oral route of administration is preferred.

Parenteral routes of administration provide the desired activity at the appropriate equivalent dose, as described above. Thus, the present method provides intravenous injection or infusion and subcutaneous injection. Regardless of the route of administration selected, the anti-PACVIS biologue is formulated into pharmaceutically acceptible dosage forms by conventional methods known to the pharmaceutical art.

When powders, pastes or gels are required, the anti-PACVIS biologue is conveniently formulated by mixture into conventional compositions. In the case of parenteral administration, sterile solutions for injection or infusion are prepared in accordance with readily available techniques. Similar sterile solutions are used for compositions in nasal administration.

The various carboxyl containing anti-PACVIS agents are all employed in any conventional, pharmaceutically acceptable form. Thus, these agents are optionally employed as free acids, esters, or salts.

The use of the anti-PACVIS biologue is, by a further embodiment of the present invention, undertaken concomitantly with other forms of conventional therapy for a PACVIS. Such other forms of conventional therapy include, for example, the various chemical therapies described in Goth et al., cited above. When such combination therapies are employed, significant anti-PACVIS effects are often obtained with reduced effective dosages of the anti-PACVIS biologue agent employed herein.

In accordance with this further embodiment of the present invention, there are provided novel pharmaceutical compositions for anti-PACVIS therapy. These novel compositions consist of combinations of two or more active agents, one such agent being an instant anti-PACVIS biologue, and the second and further agents being the heretofore known agents having the vasodilating effect. Such previously known vasodilating agents include those known as adrenergic vasodilators, direct vasodilators, and coronary vasodilators. Adrenergic vasodilators include known medicaments such as nylidrin, isoxsuprine, and isoproterenol. Direct vasodilators include other known medicaments such as hydralazine, diazoxide, minoxidil, and sodium nitroprusside. Additionally, the anti-PACVIS biologues may be combined with α or β adrenergic blocking drugs. See Goth et al. supra, pp. 89–114. The α adrenergic blocking drugs include, for example, prazosin and β adrenergic blocking drugs include propranolol. Such novel compositions are advantageously used in arresting a PACVIS, often permitting a reduced dosage of the instant anti-PACVIS agent than that which would be required were it the sole therapy for arresting or preventing the PACVIS.

In these novel pharmaceutical compositions, the instant anti-PACVIS biologue is employed for each unit dosage in an amount equal to the amount of the instant anti-PACVIS biologue were it the sole therapy down to an amount not less than 50 percent thereof. The other conventional anti-PACVIS agent or agents are present therein at the known amounts employed in the treatment to accomplish vasodilation.

Moreover, the present invention further provides compositions of the instant anti-PACVIS biologues exhibiting extraordinary convenience as a result of the topical activity of these agents in the treatment of PACVIS. Employed in these novel powder, paste, cream, or gel compositions are conventional ingredients to obtain the desired constituency of each composition except for the anti-PACVIS biologue.

Such powders, pastes, creams, or gels contain an effective amount of the anti-PACVIS biologue such that an application of a predetermined quantity of the powders, pastes, or gels to the localized area result in the desired anti-PACVIS effect. Such powders, pastes, or gels are formulated by conventional means as is known in the art, and particularly include the combination of an instant anti-PACVIS biologue with a conventional carrier (for example, powders: lactose, magnesium stearate, starch, talc; paste: stearic acid, glyceryl monostearate, cold cream; gel: polyoxethylene glycol; creams: spermacet, cetyl alcohol, stearic acid.) Such powders, pastes, creams or gels are particularly useful in the topical treatment of PACVIS secondary to functional peripheral diseases as described above.

Similarly, the instant invention relates to the further liquid composition comprising the anti-PACVIS biologue in solutions adapted for nasal administration. In accordance with such novel compositions, the instant anti-PACVIS biologue is present in the conventional sterile solution at a concentration such that a predetermined volume of the administered drops or aerosol contains an amount of the anti-PACVIS biologue effective to exert the desired anti-PACVIS effect on contact with the nasal tissues.

Foregoing novel compositions are preferably provided in unit dosage or package dosage forms, where the composition consists of an amount of each pharma-

cological agent required for a single dose or a predetermined series of doses over some predetermined interval of time. For combination therapies such unit or package dosages, therefore, may consist of a single pharmaceutical entity, containing therewithin both agents or a paired or otherwise ordered series of such discrete entities containing these agents seperately. Hence, within the ambit of the novel pharmaceutical compositions provided herein are those which would include packages containing a multiplicity of discrete pharmaceutical entities in an ordered way for the administration of these novel compositions over a predetermined period of time. For example, by a preferred embodiment of the present invention such novel compositions would include discrete pharmaceutical entities containing lesser or greater amounts of the novel anti-PACVIS biologue at the time therapy is initiated with gradually increasing or decreasing amounts of the instant anti-PACVIS biologue in discrete pharmaceutical entities intended for administration subsequently as therapy progresses.

Finally, for the anti-PACVIS biologues indicated above as orally active, there are provided in accordance with the present invention feeds and feed premixes containing amounts of the instant anti-PACVIS biologue which, when present in the animal's feed, is at a concentration effective to exert the desired anti-PACVIS effect. Such feed and feed premixes are made in accordance with readily known and available techniques particularly useful in the treatment of animals where the PACVIS compromise the animal's value. Examples of a PACVIS which compromises the value of an animal include heartworm disease in dogs and aneurysms in turkeys.

Thus, the method provided by the present invention provides for the systemic administration to an animal in an amount of an anti-PACVIS agent effective to arrest or prevent a PACVIS. The anti-PACVIS agent contemplated for use in the present invention feeds and feed premixes are those compounds known in the prior art and described in the aforementioned U.S. patents.

Examples of preferred anti-PACVIS bis chromones are generically represented by formula I,

wherein R_1, R_2, R_3, R_4, R_5, and R_6 are hydrogen, halogen (chloro, bromo, or iodo), lower alkyl (preferably alkyl of one to four carbon atoms, inclusive), hydroxy, or lower alkoxy (preferably alkoxy of one to four carbon atoms, inclusive);

wherein X is straight or branched chain polymethylene of three to seven carbon atoms, inclusive, $-CH_2-CH=CH-CH_2-$, $-CH_2-CH_2-O-CH_2-CH_2-$, $-CH_2-CO-CH_2-$, $-CH_2-(o-Ph)-CH_2$;

wherein o—Ph is 1,2—phenylene, $-CH_2-C(CH_2OH)(CH_2Cl)-CH_2-$, $-CH_2-CH(OH)-CH_2-$, or $-CH_2-CH(OH)-CH_2-O-CH_2-CH(OH)-CH_2-$; and the salts, esters, and amides thereof.

Preferred as anti-PAVCIS bis chromones in accordance with the present invention are DSCG and the various other salt and ester forms thereof, which compounds are incorporated here by reference from U.S. Pat. No. 3,419,578.

Preferred among the anti-PACVIS oxamates are the oxanilic acid derivatives represented by formula II and the phenylene dioxamic acid derivatives represented by formula III;

wherein R_1 is hydrogen, a pharmacologically acceptable cation or alkyl, preferably alkyl of one to 12 carbon atoms, inclusive;

wherein one of R_2, R_3, R_4, R_5, and R_6 is hydrogen or cyano;

wherein a second and a third of R_2, R_3, R_4, R_5, and R_6 are selected from the group consisting of hydrogen, nitro, amino, halo (fluoro, chloro, bromo, or iodo), alkyl (preferably alkyl of one to four carbon atoms, inclusive), hydroxy, alkoxy (preferably alkoxy of one to four carbon atoms, inclusive), and trifluoromethyl being the same or different, and

wherein the remainder of R_2, R_3, R_4, R_5, R_6 are hydrogen. More particularly those compounds of formulas II and III wherein R_1 is ethyl or protonated trimethamine and R_3 is cyano and R_6 (II) or R_5 (III) is chloro, the other variables being hydrogen are preferred.

The present invention thus provides a surprising and unexpected method of use and unexpectedly convenient and efficacious compositions of matter for a class of pharmacological agents previously known to be useful for unrelated pharmaceutical and other purposes.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The advantageous effects of anti-PACVIS biologues in accordance with the present invention are demonstrated by the experimental results, reported hereinafter, which are illustrative (but not limiting) as to the operation of the novel methods described above.

EXAMPLE I

The reduction of myocardial infarct size as measured by the effects on infarct size after experimental coronary artery occlusion of lodoxamide, N,N'-(2-chloro-5-cyano-n-phenylene)dioxamic acid, (as its bis-tris(hydroxymethyl)aminomethane salt).

Following the procedure of DeBoer, W. E. et al., *Proc. Natl. Acad. Sci.* U.S.A., vol. 77, no. 10, pp. 6119-6123 (October, 1980) Medical Sciences, the anti-PACVIS activity of lodoxamide is assessed. The following experiment is undertaken.

Twenty-two barbiturate anesthetized dogs are treated to receive high left anterior descending coronary artery occlusions. Ischemic bed size or area at risk of developing necrosis (AR-R) is determined before treatment by injection of 99m Tc labeled albumin microspheres with post-mortem autoradiography. The ischemic zone appears as a cold spot image. A second area at risk is determined at the time of sacrifice (AR-D) by use of an in vivo left atrial injection of thioflavin S (a fluorescent dye which stains myocardium receiving flow yellow-green, but does not stain ischemic tissue). Infarct size (IS) is determined six hours after coronary occlusion by triphenyltetrazolium staining of 5 mm transverse slices of the left ventricle. Thirty minutes after left anterior descending coronary occlusion, animals are randomized to controls (12 dogs receiving 0.9 percent saline I.V.) or lodoxamide, N,N'-(2-chloro-5-cyano-n-phenylene)dioxamic acid, (as its bis-tris-(hydroxymethyl)aminomethane salt) therapy (10 dogs receiving 20 mg per kg per hour by continuous I.V. drip). AR-R, AR-D, and IS are expressed as percentage of the left ventricle before occlusion. Infarct size is also expressed as a percentage of the area at risk. The results are shown in the table below.

TABLE I

	Controls	Lodoxamide THAM Salt	P
AR-R	28.7 + 2.6	25.3 + 3.7	NS
AR-D	28.9 + 2.5	25.2 + 3.1	NS
IS	20.0 + 2.7	13.8 + 3.2	.002
IS/AR-R	104.5 + 3.8	54.5 + 11.0	<.01
IS/AR-D	103.8 + 3.4	54.8 + 8.2	<.01

The results of Table I indicate the oxamate, lodoxamide induces a significant protective action on ischemic myocardium by showing a significant reduction in infarct size.

A further experiment indicates the prevention of necrosis by the oxamate, lodoxamide in a prophylactic manner in a manner similar to Example I.

EXAMPLE II

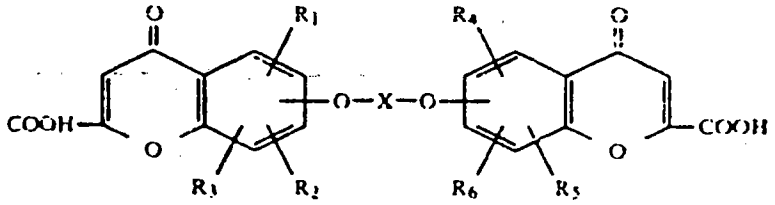
Fourteen dogs are treated to receive occlusion of the proximal left circumflex coronary artery. Ischemic bed size or area at risk of developing necrosis (AR-R) is determined before treatment by injection of 99m Tc labeled albumin microspheres with postmortem autoradiography. A second area at risk is determined at the time of sacrifice (AR-D) by use of an in vivo left atrial injection of thioflavin S (a fluorescent dye which stains myocardium receiving flow yellow-green, but does not stain ischemic tissue) in a manner similar to Example I. The animals are randomized to controls (9 dogs) or lodoxamide therapy (8 dogs receiving 20 mg/kg/hour times two infused I.V. during the period starting 30 minutes prior to and throughout 90 minutes of complete occlusion, followed by reperfusion). Infarct size (IS) is determined 24 hours after the 90 minute occlusion-fusion. The results are shown below in a manner ar to that described for Example I. In other words, the following Table II shows infarct size determined as a percent of the area at risk or as a percent of the total left ventricle.

TABLE II

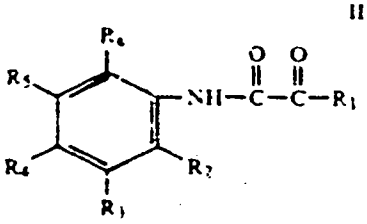
	Control	Lodoxamide THAM Salt	P
AR-R	45.3 + 2.8	22.8 + 2.8	0.001
AR-D	42.8 + 1.7	43.1 + 3.6	NS
IS	19.5 + 1.5	9.7 + 1.0	0.001

The results in Table II show the oxamide therapy occasions a decrease in infarct size.

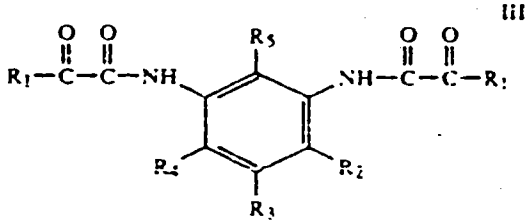
FORMULAS



I



II



III

I claim:

1 In a method of preventing or treating a pathological cardiovascular ischemic state (PACVIS) in an animal exhibiting or susceptible to development of said PACVIS with one or more known vasodilating agents selected from the group consisting of coronary vasodilating agents including nitroglycerin and isosorbide dinitrate, and direct vasodilating agents including hydralazine, diazoxide, minoxidil, and sodium nitroprusside, the improvement which comprises:

concomitantly administering an amount of an anti-PACVIS biologue equal to the amount of the instant anti-PACVIS biologue were it the sole therapy, down to an amount not less than 50 percent thereof, which, together with said known vasodilator agent, is effective to prevent or arrest said PACVIS.

2. A pharmaceutical composition in a unit dose form, for preventing or treating a pathological cardiovascular ischemic state (PACVIS) comprising one or more known coronary or direct vasodilating agents and:

an amount of an anti-PACVIS biologue equal to the amount of the instant anti-PACVIS biologue were it the sole therapy, down to an amount not less than 50 percent thereof, which, together with said known vasodilating agent or agents, in an effective unit dose to prevent or arrest said PACVIS.

* * * * *

United States Patent [19]

Cordes et al.

[11] **4,156,736**

[45] **May 29, 1979**

[54] **SUPERSATURATED ISOSORBIDE DINITRATE SOLUTION, PROCESS FOR ITS PRODUCTION AND ITS USE**

[75] Inventors: **Günter Cordes; Ulrich Münch,** both of Leichlingen; **Ewald Giesselmann,** Monheim, all of Fed. Rep. of Germany

[73] Assignee: **Sanol Schwarz-Monheim GmbH,** Monheim, Fed. Rep. of Germany

[21] Appl. No.: **798,639**

[22] Filed: **May 19, 1977**

[30] **Foreign Application Priority Data**

May 28, 1976 [DE] Fed. Rep. of Germany 2623800
Dec. 29, 1976 [DE] Fed. Rep. of Germany 2659393

[51] **Int. Cl.**[2] **A61K 31/34**

[52] **U.S. Cl.** **424/285**

[58] **Field of Search** 424/285, 180

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,911,137	10/1975	Miki et al.	424/319
3,972,995	8/1976	Tsuk et al.	424/28

Primary Examiner—Stanley J. Friedman
Attorney, Agent, or Firm—Hammond & Littell

[57] **ABSTRACT**

Supersaturated aqueous to organic solvent solution of isosorbide dinitrate, process of preparation at elevated temperatures, and use of the supersaturated solutions for the production of infusion solutions.

13 Claims, No Drawings

SUPERSATURATED ISOSORBIDE DINITRATE SOLUTION, PROCESS FOR ITS PRODUCTION AND ITS USE

BACKGROUND OF THE INVENTION

Isosorbide dinitrate (ISD) has been given orally like other nitric acid esters for angina pectoris in the form of tablets or capsules with good results for a long time. Recently it has been shown that apart from this traditional indication ISD can also be used for the following diseases: for heart insufficiency of the left ventricle, for recent myocardinfarct as well as for incipient edema of the lungs.

For the preceding indications the parenteral application offers advantages compared with the oral application since

- the patients with the aforementioned diseases are in hospitals;
- a correct, controlled dosage by infusion is necessary; and
- when parenterally applied the metabolism of the active substance during the first passage through the liver is avoided, which leads, as is well known, to a decomposition of essential amounts of active substance to mononitrates and isosorbide when orally applied.

When ISD is parenterally applied, dosage should be made up individually according to the acuteness of the respective case. The ISD concentration in ampules for the production of infusion solutions aimed at by doctors should be 1 mg/ml (= g/l), 2 mg/ml (= 2 g/l) or more, since in this manner.

- even the lowest possible starting concentration at the beginning of a treatment could be adjusted in the infusion solution;
- a sufficiently high concentration for the treatment could be attained without applying very large liquid amounts; and
- the calculation of concentrations would be considerably simplified by a simple ratio of numbers (e.g., 1 mg ISD/ml).

In general, the lowest concentration with which therapy can be started is regarded as 5 mg ISD/250 ml infusion solution. If ampules with ISD solutions having a concentration of 1 mg/ml were available, 5 ml of these ISD solutions would have to be diluted to 250 ml infusion solution. Then the dosage could be increased so that 10 mg ISD or even more a day could be applied to the patients.

On the basis of experiments preceding the invention (examples 1 to 2) the production of an aqueous ISD solution having a concentration of 1 mg/ml seemed to be impossible. At room temperature a saturation value of about 0.7 g ISD/1 was found. These experiments were carried out in the presence of solid ISD in a manner which is usual to find out saturation values; ISD was dissolved in water up to saturation at room temperature or it crystallized from an supersaturated solution which had been cooled to room temperature. The results correspond to published data. From the following table 1 there follows that the older published data (caused by inexactness) vary within a broad range and in the meantime this range has been limited to limits of about 0.5 and 0.7 g/l so that this range has been corrected.

Table 1

solubility of ISD in water (g/l)	Year	Quotation
2	1959	Med. Prom. SSSR 13 (1959) 18 - 20 according to CA 54 (1960) Quotation 8647 h
1.1	1968	Merck Index (1968) 593
0.001089	1968	Merck Index (1968) 593
<0.5	1975	Anal. Profiles Drug Subst. 4 (1975) 231
0.68	1975	Needleman, Organic Nitrates, Springer (1975) 17

OBJECTS OF THE INVENTION

An object of the present invention is to obtain a supersaturated aqueous isosorbide dinitrate solution having a content of isosorbide dinitrate in the range of more than the saturation value at room temperature temperature up to 2.5 g/l.

This and other objects of the invention will become more apparent as the description thereof proceeds.

DESCRIPTION OF THE INVENTION

However, the inventors have surprisingly found out that it is possible to produce ISD solutions having concentrations beyond the saturation value at room temperature when the production is carried out in the absence of solid ISD. It is surprising and useful that such supersaturated aqueous ISD solutions can also be used for therapeutical purposes since they are stable in an unforeseeable manner so that they can be stored without any changes for long periods (at least for months). This is especially surprising since it was not possible to fill supersaturated solutions into containers, e.g., ampules, without any crystallization on a technical scale unless the solutions, the ampules and the whole filling equipment were maintained at an elevated temperature. The use of supersaturated aqueous ISD solutions for the production of, e.g., infusion solutions is absolutely simple since in such cases the said supersaturated ISD solutions are diluted.

One embodiment of the invention concerns an supersaturated aqueous ISD solution.

This solution may contain ISD in the range of beyond the saturation value at room temperature up to 2.5 g/l, e.g., 1.0 or 2.0 g/l.

According to the invention the supersaturated aqueous ISD solution may in addition contain substances, e.g., sodium chloride, which are usual for isotonic solutions.

When according to the invention an supersaturated aqueous ISD solution is produced, ISD is completely and according to a concentration beyond the saturation value at room temperature dissolved in an aqueous medium at a raised temperature, the solution is filled into containers (if desired after filtration) at a raised temperature, the containers are closed and then cooled. Preferably ampules are used as the said containers.

It is possible to carry out the process at a raised temperature of at least 50 degrees centigrade, e.g., of at least 80 degrees centigrade.

It is possible to produce a solution having an ISD concentration of 1 g/l at at least 80 degrees centigrade; then the process including the filling is carried out at at least 50 degrees centigrade.

It is possible to combine ISD with water in a ratio of 1:1,000 and to increase the temperature to at least 80

degrees centigrade while stirring. When a clear solution has resulted, the said solution is maintained at a temperature of at least 50 degrees centigrade, filtrated through a suitable filter, if desired, and filled into ampules with any content. Then it is possible to sterilize the ampules in the usual manner in superheated steam according to the methods of the Deutsches Arzneibuch.

When the solution has been filled into the said containers and ampules, respectively, and sealed it is possible to heat the solution for, e.g., 15 minutes to at least 95 degrees centigrade, preferably 121 degrees centigrade.

However, in the event of particular diseases, it is necessary to give the patients even larger amounts of ISD by infusion than it is possible with supersaturated ISD solutions based on water as a single solvent.

According to another embodiment of the invention this problem is solved by an supersaturated aqueous ISD solution which contains a physiologically acceptable organic solvent (which is preferably suitable for infusions), e.g. alcohols, preferably polyhydric aliphatic alcohols, more preferably C_{3-4} -diols.

The solution according to the invention may contain 0.5 or more, preferably 5, 10, 20 or 50 or more, and more preferably 100% organic solvent based on the total amount of organic solvent and water.

The organic solvent is 1.2-proxyleneglycol, for example, which is preferably present in an amount of 100% based on the total amount of organic solvent and water. The ISD content may be in the range of beyond the saturation value at room temperature up to 30 g/l, e.g., up to 20 g/l.

For the production of ISD solution according to the invention ISD is completely and according to a concentration beyond the saturation value at room temperature dissolved at a raised temperature in a liquid medium which contains water and up to 100% of a physiologically acceptable organic solvent based on the total amount of organic solvent and water, the solution is (if desired after filtration) filled into containers at a raised temperature, the containers are closed and then cooled. It is possible to dissolve ISD at an elevated temperature of at least 50 degrees centigrade, e.g., about 80 degrees centigrade or more and to carry out the other steps including the filling at a temperature of at least 30 degrees centigrade, e.g. about 40 degrees centigrade or more.

Preferably the containers containing the solution are heated for at least 15 minutes to at least 95 degrees centigrade, preferably about 121 degrees centigrade.

It is possible to use 1,2-propyleneglycol as an example of a liquid medium. Further, it is possible to produce at about 80 degrees centigrade or more a solution having an ISD concentration of e.g. 20 g/l; then the process including the filling may be carried out at e.g. at least 30 degrees centigrade, e.g. about 40 degrees centigrade or more.

According to the invention special care is taken that the ISD solution doesn't become cold during the complete process of production, filtration and filling, which is different from the usual practice for the production of solutions which are filled into containers, e.g. ampules. The equipment used for production and filling is therefore best provided with special tempering means.

Ampules are suitable containers; they may be sterilized according to the methods of Deutsches Arzneibuch.

ISD solutions according to the invention may be used for the production of infusion solutions.

In the following the invention is described by examples in more detail.

EXAMPLE 1

Finely powdered ISD was shaken together with water at 24 degrees centigrade in a glass bottle with an automatic shaking apparatus for several hours. The ISD amount fed was so great that even after shaking a considerable excess of undissolved ISD remained. Then the undissolved ISD was filtrated off; the ISD content of the clear solution was examined by means of the phenol/disulfonic acid method. The evaluation was made by comparison with a standard solution which contained pure ISD. An ISD saturation concentration of 0.6858 mg/1.0 ml solution was found.

Details of the Experiment

Standard weight 39.94 mg/50 ml (Acetone/water mixture);

For the examination 0.5 ml of this standard solution were used;

Extinction of the standard solution = 0.396;

0.5 ml of the solution to be examined for comparison;

Extinction of the solution to be examined = 0.340.

EXAMPLE 2

Finely powdered ISD was stirred with a magnetic stirrer at 50 degrees centigrade in water for one hour. Then the solution was left at room temperature for 24 hours and undissolved ISD was filtrated off. An ISD saturation concentration of 0.76 mg/ml was found in the filtrate.

Details of the Experiment

Standard weight 39.65 mg/50 ml (Acetone/water mixture);

Extinction of the standard solution = 0.416;

Extinction of the solution to be examined 32 0.396.

EXAMPLE 3

1000 ml distilled water were added to 1 g ISD and 9 g sodium chloride with stirring. The mixture was heated to about 50 degrees centigrade until a clear solution resulted. The solution was filtrated and filled into ampules. The ampules were closed and sterilized in superheated steam at 121 degrees centigrade for about 15 minutes.

After the production the ISD content of some samples of these ampules was examined. Some other samples were stored in a refrigerator at 10 degrees centigrade and in a deep freezer, respectively, at minus 20 degrees centigrade for some time and then analyzed. Finally a sample was stored at room temperature for a long time; then its ISD content was examined. No samples showed crystals.

A quantative thin layer chromatography analyzing method was developed to examine the ISD. This method guaranteed that only undecomposed ISD was taken into consideration since possible decomposition products were separated from the pure ISD by chromatography. With this specific analyzing method it was possible to find out whether changes had appeared during the production or the storage. The results of the examinations are listed in the following table 2.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,156,736

DATED : May 29, 1979

INVENTOR(S) : Gunter Cordes, Ulrich Munch and Edwald Giesselmann

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Col.	Line	
1	34	"(= g/1)" should be --(= 1 g/1)--
3	25	"1.2" should be --1,2--
4	40	"320.396" should be --0.396--
5	Table 3	line 4 "965" should be --966--
5	60	"changein" should be --change in--
6	34	"The" should be "A"

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Col.	Line	
6	11	delete [desired supersaturation occurs] and insert --selected amount of isosorbide dinitrate is completely dissolved--
6	45	same as above
3	15	"an supersaturated" should be --a supersaturated--

Signed and Sealed this

Twentieth Day of *May 1980*

[SEAL]

Attest:

SIDNEY A. DIAMOND

Attesting Officer *Commissioner of Patents and Trademarks*

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,156,736 Page 1 of 2

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Signed and Sealed this

Twentieth Day of *May 1980*

[SEAL]

Attest:

SIDNEY A. DIAMOND

Attesting Officer *Commissioner of Patents and Trademarks*

EXCLUSIVITY SUMMARY

NDA # 20-727 SUPPL # N/A HFD # 110

Trade Name BiDil

Generic Name isosorbide dinitrate and hydralazine HCl

Applicant Name NitroMed, Inc.

Approval Date, If Known June 23, 2005

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

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.

N/A

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:

N/A

d) Did the applicant request exclusivity?

YES ☒ NO ☐

June 10, 2005 submission

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

3 years

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

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

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

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 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. N/A

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 ☒ NO ☐

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

NDA# 08-303 Apresoline (hydralazine HCl)

NDA# 12-093 Isordil (isosorbide dinitrate)

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs 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:

N/A

(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:

N/A

(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:

N/A

(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:

The African-American Heart Failure Trial (A-HeFT)

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:

IND 41,816

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:

N/A

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"):

The African-American Heart Failure Trial (A-HeFT)

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 # 41,816 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? N/A

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! 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 ☒

If yes, explain:

N/A

Name of person completing form: Dianne Paraoan
Title: Regulatory Health Project Manager, HFD-110
Date: June 21, 2005

Name of Division Director signing form: Norman Stockbridge, M.D., Ph.D.
Title: Acting Director, Division of Cardio-Renal Drug Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Norman Stockbridge
6/23/05 12:44:42 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 20-727 Supplement Type (e.g. SE5): N/A Supplement Number:

Stamp Date: December 23, 2004 Action Date: June 23, 2005

HFD- 110 Trade and generic names/dosage form: BiDil (isosorbide dinitrate 20 mg and hydralazine HCl 37.5 mg) tablets

Applicant: NitroMed, Inc. Therapeutic Class: Vasodilator

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s):one

Indication #1: treatment of chronic heart failure as an adjunct to standard therapy in black patients to improve survival and prolong time to hospitalization for heart failure.

Is there a full waiver for this indication (check one)?

☑ **Yes: Please proceed to Section A.**

☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☑ **Too few children with disease to study**
☐ **There are safety concerns**
☑ **Other: There is considerable doubt that heart failure in children is close enough to the heart failure in adults to make such as study likely to succeed.**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____

Reason(s) for partial waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Adult studies ready for approval**
☐ **Formulation needed**
☐ **Other:_____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Dianne C. Paraoan
Regulatory Project Manager

cc: NDA 20-727
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

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

/s/

Dianne Paraoan
6/6/05 11:54:50 AM

16. DEBARMENT CERTIFICATION

NitroMed, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

Michael Sabolinski, M.D.
Senior Vice President, Clinical Development and Regulatory Affairs

MEDCO
RESEARCH, INC.

June 26, 1996

DEBARMENT CERTIFICATION

In support of this New Drug Application for BiDil®(hydralazine hydrochloride and isosorbide dinitrate) Tablets and in accordance with the Generic Drug Enforcement Act of 1992, Medco Research, Inc., certifies that it did not and will not use, in any capacity, the services of any person (including a company or partnership), debarred under subsections (a) or (b) [Section 306(a) or (b)] of the Food, Drug, and Cosmetic Act.

Anne McKay
Director, Regulatory Affairs

P.O. BOX 13886 • RESEARCH TRIANGLE PARK, NC 27709 • PHONE: (919) 549-8117 • FAX: (919) 549-7515

3.2 Financial Disclosures

In accordance with 21 CFR Part 54, this section contains a list of all investigators and sub-investigators, who have been listed on Forms FDA 1572, and who have signed financial disclosure forms in accordance with 21 CFR Parts 54.1 to 54.6. Each of these investigators has signed a Form FDA 3454 attesting to the absence of any significant equity interest with the sponsor company. Therefore, as required, NitroMed, Inc. has included herein a signed Form FDA 3454, attesting to such for all investigators and sub-investigators.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: February 28, 2006.

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	List Attached	

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Manuel Worcel, MD	Chief Medical Officer
FIRM / ORGANIZATION	
NitroMed, Inc.	
SIGNATURE	DATE
	12/18/04

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Site	Affiliation	Principal Inv.	Coord	Coord 2	Coord 3	Sub I (1)	SubI (2)	SubI (3)	SubI (4)	SubI (5)	SubI (6)	SubI (7)	SubI (8)	SubI (9)
1	Meharry Medical College	Theodore Addai, MD, FACC												
2	Minneapolis VA Medical Center	Inder S. Anand, MD												
3	Plaza Medical Group	Jerome Lyman Anderson, MD												
4	Midatlantic Cardiovascular Associates, PA	Toni L. Bransford, MD												
6	East Carolina School of Medicine	Joseph Babb, MD												
7	Hennepin County Medical Center	Steve Goldsmith, MD												
9	Cardiac Disease Specialists, P.C.	Kenneth Taylor, MD / Lance Berger M.D.												
0	Cardiovascular Research Institute of Dallas	Martin R. Berk, MD												
2	The Heart Group, PC	Christopher S. Brown, MD												
3	Cardiology Associates of Mobile, Inc.	Kenneth M. Burnham, MD												
4	University of North Carolina	Kirkwood F. Adams, JR												
5	Jerome O. Spruill, MD	Jerome O. Spruill, MD												
6	Durham VA Medical Center	Frederick R. Cobb, MD												
8	Henry Ford Health System	Barbara Czerska, MD												
9	University of Pennsylvania Health Systems	Shashank DeSai, MD												
0	River Cities Cardiology	D. Marty Denny, MD												
1	University of Illinois at Chicago	Stephanie H. Dunlap, DO												
2	Dallas VAMC	Susan A. Mayer												
3	Med-Tech Research	Luis A. Campos, MD												
5	Xavier University Clinical Trials Unit	Keith C. Ferdinand, MD												
6	Southeast Medical Associates	Richard G. Berry, MD												
7	University of Maryland Hospital	Stephen Scott Gottlieb, MD												
8	Ratan L. Tiwari Incorporated	Betty Grant-Anderson												
9	Bertram Anthony Graves, MD	Bertram Anthony Graves, MD												
2	Cardiology Group P.C.	Dinesh K. Gupta												

Affiliation	Principal Inv.	Coord	Coord 2	Coord 3	Sub I (1)	SubI (2)	SubI (3)	SubI (4)	SubI (5)	SubI (6)	SubI (7)	SubI (8)	SubI (9)
Cardiology and Medicine Clinic, PA	Joe L. Hargrove, MD												
General K. Hilliard, MD	General K. Hilliard, MD												
Medical College of WI-Div. Of Cardiovascular Medicine	Michael J. Ptacin, MD												
Medical College of WI-Div. Of Cardiovascular Medicine	Michael J. Ptacin, MD												
Advocate Health Care - Sykes Center	John Sobolski, MD												
Cedars-Sinai Medical Center	Steven Khan, MD												
North Philadelphia Health System, St. Joseph's Hospital	David E. Knox, MD												
University of Florida	Daniel Pauly, MD												
DMI Health Care Group, Inc	Merrill Krolick, DO												
Mount Sinai Medical Center	Marrick Kukin, MD												
North Houston Heart Center	Bruce Lachterman, MD												
Vanderbilt University Medical Center	Don Barak Chomsky, MD												
North General Hospital	Myo Maw												
The Stern Cardiovascular Center, PA	Frank A. McGrew, III, MD												
Midatlantic Cardiovascular Associates, PA	Henry Meilman, MD												
University of Cincinnati	Lynne E. Wagoner, MD												
State University of New York at Brooklyn	Louis Salciccioli / Judith Mitchell, MD												
North Broward Hospital District	John J. Rozanski, MD												
Cardiology Clinic of San Antonio	Theron C. Toole II, MD												
Eastmoreland Internal Medicine	Thomas E. Motley, MD												
Morehouse School of Medicine, Clinical Research Center	Elizabeth Ofili, MD												
Maricopa Medical Center	Jesus Hernandez, MD / Rajah Patel, MD												
Saint Thomas Research Institute	Douglas Pearce, MD												
Krannert Institute of Cardiology	Irmina Gradus-Pizlo, MD												
Newark Beth Israel Medical Center, Division of Cardiology	Hillel S. Ribner, MD												

	Affiliation	Principal Inv.	Coord	Coord 2	Coord 3	SubI (1)	SubI (2)	SubI (3)	SubI (4)	SubI (5)	SubI (6)	SubI (7)	SubI (8)	SubI (9)
	Heart and Vascular Institute of Florida	Gregg T. Schuyler, MD, PhD, FACC												
	Tulane University Health Sciences Center	Lawrence O' Meallie, MD / Frank W. Smart, MD / Muhammad Khalid, MD												
	Baylor College of Medicine	Guillermo Torre-Amione, MD, PhD												
	Dr. Kermit Brown, Medical Office	Kermit Brown, MD FACC												
	Atlanta Veterans Affairs Medical Center	W. Robert Taylor, MD, PhD												
	Oklahoma University Health Sciences Center	Udho Thadani, MD												
	Leonard Bass, MD	Leonard Bass, MD												
	Heart Associates	Michael N. Rubinstein, MD												
	Birmingham VA Medical Center	Gilbert J. Perry, MD												
	Boston Medical Center	Flora Sam, MD / Daniel Forman, MD												
	Ford Research Institute, PA	Daniel Phillips, MD												
	Providence Family Practice and Urgent Care Center, PA	Augustine W. Onwukwe, MD												
	MetroHealth Medical Systems	Karen Kutoloski, DO												
	Cranford L. Scott, MD, Inc Office	Cranford L. Scott, MD												
	Grady Memorial Hospital and Morehouse School of Medicine Clinical Research Center	Adefisayo Oduwole, MD												
	Central Florida Cardiology Group, PA	Anil Kumar, MD												
	John D. Dingell VA Medical Center	John M. Flack, MD, MPH												
	University of Florida Health Science Center/Jacksonville	Alan B. Miller, MD												
	VA Tennessee Valley Healthcare System	Javed Butler, MD, MPH												
	University of Texas Southwestern Medical Center	Clyde W. Yancy, MD												
	Brevard Cardiology Physicians, PA	Khalid H. Sheikh, MD												
	Howard Univeristy Hospital	Charles L. Curry, MD												
	Arkansas Primary Care Clinic	Derek Lewis, MD												
	University Hospitals of Cleveland	Ileana L. Pina, MD												

te	Affiliation	Principal Inv.	Coord	Coord 2	Coord 3	Sub I (1)	SubI (2)	SubI (3)	SubI (4)	SubI (5)	SubI (6)	SubI (7)	SubI (8)	SubI (9)
	Louis Stokes VA Medical Center	Mark Dunlap, MD												
	Cooper Green Hospital	Rick Player, MD												
	Dayton Heart Center	Gary Jay Fishbein, MD												
	Heart and Vascular Clinic	Ghiath Mohammad Mikdadi, MD												
	Cardiology Associates, PC	Susan K. Bennett, MD												
	Foundation Research	Michael McIvor, MD												
	University of Nebraska Medical Center	Richard S. Rigmaiden III, MD												
	St. Vincent's Catholic Medical Center	Marc Klapholz, MD												
	Loma Linda University Medical Center	J. James Heywood, MD												
	USC LA County and USC Medical Center	Uri Elkayam, MD												
	Virginia Commonwealth University Health System / MCV Hospitals and Physicians	Michael L. Hess, MD												
	University of Mississippi Medical Center	Charles K. Moore, MD												
	Omaha VA Medical Center	Richard S. Rigmaiden III, MD												
	University of Chicago	Roberto Lang, MD												
	Baltimore Heart Association, PA	Ramona Gelzer Bell, MD												
	Cardiac Centers of Louisiana, LLC	Jalal Kamal Ghali, MD												
	Arkansas Heart, PA	Steven Wayne Hutchins, MD												
	University of Michigan Medical Center	William E. Chavey, MD / John M. Nicklas, MD												
	Medical University of South Carolina	Adrian VanBakel, MD												
	Rush Heart Failure and Cardiac Transplant Program	Alain L. Heroux, MD												
	The Greater Ft. Lauderdale Heart Group Research	Alan L. Niederman, MD												
	Temple University Hospital	Shelley Hankins, MD												
	Duke University Medical Center	Lawrence Crawford, MD												
	Northwest Hospital Center	Ramona Gelzer Bell, MD												
	Yale University School of Medicine	Stuart Katz, MD												
	Lifelink Transplant Institute	Mark Weston, MD												

te	Affiliation	Principal Inv.	Coord	Coord 2	Coord 3	SubI (1)	SubI (2)	SubI (3)	SubI (4)	SubI (5)	SubI (6)	SubI (7)	SubI (8)	SubI (9)
	Central Arkansas Veterans Healthcare System / University of Arkansas for Medical Sciences	Yamil W. Aude, MD / Jacob Joseph, MD, FACC												
	Truman Medical Center / University of Missouri-Kansas City	Mukesh Garg, MD / Peter McCullough, MD, MPH												
	Grady Health Systems / Emory University Sch. Medicine	Paul H. D'Amato, MD												
	Renaissance Clinical Research and Hypertension Clinic	Waymon Drummond												
	Washington Hospital Center	Richard H. Cooke, MD												
	SRMC - Clinical Research	David Ike, MD												
	Midatlantic Cardiovascular Associates, PA	Jeffrey L. Quartner, MD												
	Apex Cardiology Consultants	Cranford L. Scott, MD												
	Central Arkansas Veterans Healthcare System / University of Arkansas for Medical Sciences	Yamil W. Aude, MD / Jacob Joseph, MD, FACC												
	The University of Alabama at Birmingham	Jose A. Tallaj, MD												
	Wake Heart Associates	James Tift Mann, III, MD												
	South Broward Cardiology Consultants	Lawrence M. Reiss												
	Washington DC VA Medical Center	Michael Greenberg, MD												
	Alegent Health Immanuel Medical Center	Douglas B. Chapman, MD												
	Michael Reese Hospital	John Sobolski, MD												
	Leonard Chabert Medical Center	Kathy A. Hebert, MD												
	Louisiana State University Health Sciences Center	Roxane A. Townsend												
	Pioneer Medical Group-Pacific Research Management	Sanat Patel, MD												
	Jason Boutros' Medical Offices	Jason Boutros, MD												
	Kamlesh N. Dave, MD, FACC	Kamlesh N. Dave, MD, FACC												
	VA Western New York Healthcare System	Muzamil Rana												
	Cardiology, P.C.	Alain Bouchard												
	Cardiovascular Clinics P.C.	Vijay Dave, MD												
	Medical Center Cardiologist	Jesse Adams, MD												
	Diagnostic Cardiology, PA	Julius Dean, MD												

ite	Affiliation	Principal Inv.	Coord	Coord 2	Coord 3	Sub I (1)	SubI (2)	SubI (3)	SubI (4)	SubI (5)	SubI (6)	SubI (7)	SubI (8)	SubI (9)
5	W.O. Moss Regional Medical Center	Harpal Benipal, MD												
6	Miami International Cardiology consultants (MICC)	Kevin Coy, MD												
9	North Ohio Heart Center	Hassan M. Ibrahim, MD												
0	Beloit Clinic S.C.	Leo Chuks Egbujiobi, MD, FACC, FACP												
3	Medical College of Georgia	L. Michael Prisant, MD, FACC, FACP												
4	Audubon Internal Medicine Research Center	Beverly L. Harris, MD / Margaret M. Pelitere, MD												
7	Carter Cardiovascular Clinics	James E. Carter Jr. MD												
8	LSU / UMC	Karen G. Curry, MD												
9	Emory University Hospital	Andrew L. Smith, MD												
0	Washington University	Joseph G. Rogers, MD												
8	York Clinical Research	Charles F. Lovell, MD, FACP												
3	Greater Los Angelos Veterans Healthcare System	Alberta Warner, MD												
1	Grupo Medico Lafayette	Angie M. Rosado, MD												
4	Harris & Associates PC	Anthony Harris												
6	Miami International Cardiology consultants (MICC)	Ali Bazzi, MD												
8	Horizon Institute for Clinical Research	Ariel Soffer, MD												
0	Louisiana State University Health Sciences Center	Robert S. Lewis, MD												
1	Suncoast Medical Clinic	Vibhuti N. Singh, MD												
3	HealthSouth Clinical Research, LLC / Neeman Medical International	Raymond W. Workman, MD												
4	The Care Group, LLC	Mary N. Walsh, MD												
5	Winters Center for Heart Failure Research Baylor College of Medicine / Veterans Affair Medical Center	Anita Deswal, MD												
6	Southern Heart Center	Randel L. Smith, MD												
8	Garden State Cardiovascular Specialists	Jasit S. Walia, MD												
0	The Heart Group, PLLC	Douglas Pearce, MD												
3	Renstar Medical Research	Orlando Maytin, MD												
4	Cardiovascular Research Foundation of Louisiana	Denzil Louis Moraes, MD												

Site	Affiliation	Principal Inv.	Coord	Coord 2	Coord 3	Sub I (1)	SubI (2)	SubI (3)	SubI (4)	SubI (5)	SubI (6)	SubI (7)	SubI (8)	SubI (9)
16	Albert Einstein Healthcare Network	Aman Amanullah, MD												
19	Wm Jennings Bryan Dorn VA Medical Center	Alberto Saenz, MD												
50	Bendel Medical Research	Richard H. Fei, MD												
51	Creighton Cardiac Center	Claire Hunter, MD												
52	Easton Road Medical Assoc	Sanul Corrielus, MD												
54	Oklahoma Heart Institute	Alan M. Kaneshige, MD												
55	North Phoenix Heart Center	Paul L. Underwood, MD												
57	H.S. Bhatia, MD, FACC	H.S. Bhatia, MD, FACC												
58	Merced Heart Associates	Mani Nallasivan, MD												
59	North Dallas Research Associates	Muhammad Akram Khan, MD												
60	The Hoffman Heart Institute of Connecticut	Richard J. Soucier, MD												
61	Mercer Bucks Cardiology	Alan G. Stern, MD, FACC												
62	Cardiovascular Assoc of East TX	Carl Israel, MD												
66	The University of Texas Medical Branch	Ernst Schwarz, MD												
68	Lieber and Moore Cardiology Associates	Ira H. Lieber, MD, FACC												
69	Mid-State Cardiology	George Crossley, MD												
71	Horizon Institute for Clinical Research	Edwin H. Hamilton, MD / Edward J. Zelnick, MD / Stuart P. Farber, MD												
79	Mid-State Cardiology	George Crossley, MD												
80	Access Clinical Trials	Douglas Waldo, MD												
83	Delta Heart and Medical Clinic	John Olowoyeye, MD												
87	Augusta Cardiology Clinic, PC	Stephen R. Broadwater, MD												
90	Continuum Cardiac Clinical Research, LLC	Reynolds M. Delgado, MD												
92	Pacific Heart Associates	Daren Primack, MD												
93	Shah Associates, PA	Mahesh P. Shah, MD, FACC												
94	South Carolina Heart Center, PA	Rodney Harrison, MD												
95	Advanced Health Institute	Joseph A. Puma												
96	COR Clinical Research, LLC	Clinton N. Corder, PhD, MD												

Site	Affiliation	Principal Inv.	Coord	Coord 2	Coord 3	Sub I (1)	SubI (2)	SubI (3)	SubI (4)	SubI (5)	SubI (6)	SubI (7)	SubI (8)	SubI (9)
97	**Heart Care Center / Metrolina Medical Research**	Anmer Quereshi				[				]				
99	**Arrowhead Regional Medical Center Cardiology Dept**	Steven Joseph Fitzmorris, MD												

Appears This Way
On Original

8 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(5) Deliberative Process

____ § 552(b)(4) Draft Labeling

NDA REGULATORY FILING REVIEW

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

NDA #: 20-727

1. Does the application reference a listed drug (approved drug)? YES ☐ NO ☒

   If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

   YES ☐ NO ☒

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

   If "No," skip to question 4. Otherwise, answer part (b).

   (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐
   (The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

   If "Yes," skip to question 6. Otherwise, answer part (c).

   (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? YES ☐ NO ☐

   If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

4. (a) Is there a pharmaceutical alternative(s) already approved? YES ☐ NO ☒

   (***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

   If "No," skip to question 5. Otherwise, answer part (b).

   (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO ☐

(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

NOTE: *If there is more than one pharmaceutical alternative approved, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "**Yes**," skip to question 6. Otherwise, answer part (c).*

(c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES ☐ NO ☐

*If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

YES ☐ NO ☒

*If "**No**," skip to question 6.*

*If "**Yes**," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.*

(b) Is the approved drug product cited as the listed drug? YES ☐ NO ☐

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution"). This application is a combination drug product for heart failure in blacks.

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ☒

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☒

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES ☐ NO ☒

10. Are there certifications for each of the patents listed for the listed drug(s)? YES ☐ NO ☒

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☒ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s): Referencing public literature

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must* ***subsequently*** *submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?

YES ☐ NO ☒

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

YES ☐ NO ☒

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

N/A ☒ YES ☐ NO ☐

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

N/A ☐ YES ☒ NO ☐

Refer to cover letter dated December 21, 2004

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4): The sponsor did not request exclusivity.

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

YES ☒ NO ☐

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

YES ☒ NO ☐

- EITHER

The number of the applicant's IND under which the studies essential to approval were conducted.

IND# 41, 816 NO ☐

OR

A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

YES ☐ NO ☐

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES ☒ NO ☐

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

/s/

Dianne Paraoan
6/20/05 04:13:37 PM
CSO

RHPM Overview of NDA 20-727
BiDil (isosorbide dinitrate and hydralazine HCl)
June 23, 2005

Sponsor:	NitroMed, Inc.
Classification:	4S
Receipt Date:	December 23, 2004
User Fee Goal Date:	June 23, 2005
AE/AP Letter Issued:	June 23, 2005
Final Draft Labeling:	June 23, 2005

Background

BiDil is a fixed combination formulation consisting of 2 active ingredients, hydralazine HCl, a drug approved for essential hypertension and isosorbide dinitrate, approved for the prevention of angina pectoris. BiDil is to be taken orally three times a day.

On July 2, 1997, Medco Research, Inc. received a not approvable letter for BiDil for the treatment of congestive heart failure. The not approvable letter sited several medical, chemistry, and clinical pharmacology deficiencies. Since then, the sponsor, now NitroMed, Inc., has submitted a series of submissions resolving the listed chemistry and clinical pharmacology deficiencies.

After several meetings with the Division to discuss analyses of the V-HeFT I and V-HeFT II trials, it was agreed that a third trial, the African American Heart Failure Trial (A-HeFT), performed in a black heart failure population, can be conducted. Per the sponsor, the results of the A-HeFT trial demonstrate clearly the positive results with BiDil.

On December 23, 2004, NitroMed, Inc. provided the Division with a complete response to their July 2, 1997 not approvable letter. NitroMed, Inc. now seeks an indication for the treatment of heart failure in black patients.

Previous correspondence and meetings regarding the development of BiDil for the indication of heart failure:

1. Guidance Meeting, discussion about the statistical analysis of V-HeFT trial, January 11, 1991
2. Pre-IND Meeting, November 20, 1992
3. Pre-NDA Meeting, November 30, 1995
4. Teleconference, discussion of multiple-dose pharmacokinetic study, September 10, 1996
5. Teleconference, discussion of multiple-dose pharmacokinetic study, November 6, 1996
6. Pre-Advisory Committee Meeting, November 21, 1996
7. Pre-Advisory Committee Meeting, December 19, 1996
8. Post-Advisory Committee Meeting, April 22, 1997
9. Guidance Meeting, discussion of new protocol, December 12, 2000
10. Teleconference, CMC issues, January 23, 2001
11. Teleconference, discussion of revised protocol, January 24, 2001
12. Teleconference, discussion of clinical protocol, April 6, 2001
13. Teleconference, CMC issues, June 25, 2002
14. Guidance Meeting, discuss the DSMB recommendation and extension of A-HeFT trial, July 15, 2004
15. Teleconference, to inform sponsor of plans for Advisory Committee Meeting, April 7, 2005
16. Teleconference, Pre-Advisory Committee Meeting, May 2, 2005
17. Teleconference, Pre-Advisory Committee Meeting, May 6, 2005
18. Teleconference, Pre-Advisory Committee Meeting, May 13, 2005
19. Teleconference, Pre-Advisory Committee Meeting, June 2, 2005
20. Teleconference, Labeling Discussion, June 21, 2005

Office Director's Memorandum
In his memorandum to file dated June 21, 2005, Dr. Temple summarized the critical issues that were discussed during the Cardio-Renal Advisory Committee Meeting held on June 16, 2005. Critical issues were the strength of evidence supporting BiDil's overall effectiveness in the black population studied, the strength of evidence of an effect on survival and the evidence against an effect in the white population.

Medical Review
In her review dated April 15, 2005, Dr. Lemtouni stated that the A-HeFT study, despite that it was prematurely terminated for a significant reduction of mortality on BiDil and that less data was collected than planned, it was able to meet its primary endpoint of a significant favorable change in the mean of the composite score of mortality, first hospitalization for heart failure and quality of life on BiDil compared to placebo.

The safety profile of BiDil in A-HeFT was not very different from that of placebo. Given that BiDil had a beneficial effect on all-cause mortality, any adverse event no matter how severe it is, it would be relatively tolerable in this population.

The proposed indication per the label is the treatment of CHF in black patients who are either intolerant or have a contraindication to ACE inhibitor therapy, but the patients studied in the pivotal trial were not enrolled based on their intolerance or the contraindication to ACE inhibitors. Therefore, Dr. Lemtouni concluded that BiDil should be indicated in the same population in whom it was studies in the A-HeFT study.

Financial Disclosure is included in the action package and is incorporated in the Medical Review signed off on June 23, 2005.

The Integrated Summary of Safety and Effectiveness is incorporated in the Medical Review.

The Safety Update Review is incorporated into the medical review addendum dated May 17, 2005.

Statistical Review
In his review dated May 4, 2005, Dr. Hung concluded that BiDil gives a statistically significantly better mean composite score than placebo. The benefit of BiDil with respect to the composite score can be further explained by a statistically significantly smaller all-cause mortality rate ($p=0.012$) and statistically significantly smaller incidence rate of heart failure hospitalization ($p< 0.001$). The results of A-HeFT seem to provide support for the post hoc findings for black patients in V-HeFT I and II.

Dr. Hung added that a worrisome observation is that BiDil's effect on mortality appears to be entirely contributed by the patients that are not analyzed in interim analysis #2 where a data-drive sample size increase takes place. The exploratory analysis results do not provide sufficient explanation for this observation. According to the sponsor's analyses, possible differences in baseline covariates between the interim-analysis cohort and the post-interim analysis cohort do not materially impact the estimated effect of BiDil and its statistical significance.

Throughout the trial, usage of concomitant cardiovascular medications seems balanced between the treatment groups, except possibly lower usage of non-aldosterone antagonist diuretics in the patients received BiDil in the Look-2 cohort. Compared to the Look-2 cohort, the post-Look-2 cohort appears to have higher usage of ACE inhibitors or ARB and beta-blockers at Month 3. However, base on the sponsor's analysis adjusting for the six concomitant cardiovascular medication classes, the effect of BiDil does not appear to be significantly impacted.

The quality of life results show a trend in favor of BiDil but statistical significance is inconclusive (the pre-specified primary analysis gives p=0.24).

Pharmacology Review
In his first review completed April 20, 2005, Dr. DeFelice concluded that this application is approvable from the pre-clinical perspective. This application contains no new animal pharmacolodynamic, pharmacokinetic, or toxicology data, and none are needed or anticipated.

Dr. DeFelice provided labeling recommendations in his review, specifically to the Carcinogenesis, Mutagenesis, Impairment of Fertility, and Pregnancy Category sections.

In his second review dated June 20, 2005, Dr. DeFelice recommended the following language be placed in the package insert, " [ ]

Biopharmaceutical Review
In their review finalized on April 15, 2005, Drs. Hinderling and Velazquez concluded that the clinical pharmacology and biopharmaceutical issues in the not-approvable letter dated July 2, 1997 have been resolved and that the information submitted in their complete response is acceptable.

However, the Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation 1 recommended that the sponsor determine a) the involvement of CYP 450 in the metabolism of hydralazine HCl and isosorbide dinitrate and the inhibitory and inductive potential of hydralazine HCl and isosorbide dinitrate on CYP 450 in vitro using liver tissues and b) whether hydralazine HCl and isosorbide dinitrate are substrates and/r inhibitors of P-glycoprotein. The target population receives background therapy including narrow therapeutic range drugs. The identity of a significant fraction of the dose of hydralazine HCl that is systemically available has not been determined and the metabolism of hydralazine HCl could involve CYP 450. There is evidence for oxidative microsomal metabolism of hydralazine HCl. Co-administered digoxin and statins are substrates of P-glycoprotein.

Labeling recommendations are included in their review.

The Office of Clinical Pharmacology and Biopharmaceutics/ Division of Pharmaceutical Evaluation 1 recommends the following language be included in the action letter:

> The following dissolution method and specification for both isosorbide dinitrate and hydralazine HCl are recommended:
>
> 1) USP Apparatus I at 100 RPM in 900 ml of 0.05 N HCl
>
> 2) Specification not less than [ ] in 30 minutes

No Phase 4 commitments were proposed.

Chemistry Review
In his review, Dr. Raman recommended approvable from the perspective of chemistry, manufacturing, and control. On May 11, 2005, the sponsor was issued a discipline review letter outlining the information that is needed to complete this application (as noted at the end of his chemistry review and in the correspondence/telecoms/faxes section of this action package). Major deficiencies which need to be resolved include:

1. Lack of safety data (qualification) for a new degradation product [ ] which is unique to this formulation.
2. Inadequate stability data for the drug product.

In Dr. Raman's second review, dated June 21, 2005, he cited that this application is approval from the perspective of chemistry, manufacturing, and control. The sponsor provided adequate responses to our May 11, 2005 discipline review letter.

The Office of New Drug Chemistry I recommends the following language to be included in the action letter:

> Please continue to monitor the [ ] as an impurity/degradant in the release and stability testing of BiDil® tablets with a release/shelf life limit of not more than (NMT) [ ] Based on the stability data submitted, an expiration dating period of 6 months is assigned to BiDil® tablets when stored at 25°C.
>
> We remind you of your commitments provided in the June 9, 2005 submission to:
>
> 1) submit a second identification test for inclusion in the drug product specifications by July 31, 2005
>
> 2) complete work on identification of impurity/degradation products in BiDil® tablets with revised specifications, if appropriate, by August 31, 2005.

The Office of Compliance has issued an overall acceptable recommendation for all establishments on December 21, 2004.

The Environmental Assessment (EA) and the Finding of No Significant Impact (FONSI) was completed at time of original submission and approved on August 28, 1996.

No Phase 4 commitments were proposed.

DSI
According to the medical officer, Dr. Lemtouni, an inspection is not warranted. This was also concluded during the August 2, 1996 filing meeting.

Pediatric Rule
Based on the information provided in the complete response submission of December 23, 2004, the Division issued a letter granting their application 1) a waiver of pediatric studies in pediatric patients < 1 month to < 6 years of age and 2) a deferral for pediatric studies in patients' ages 6 to 16 years of age. NitroMed, Inc. was to submit a pediatric drug development plan by May 9, 2005.

On May 6, 2005, NitroMed, Inc. submitted their pediatric drug development plan and a request to reconsider granting their application a waiver from all pediatric studies. The Division, on May 25, 2005, granted this application a waiver from all pediatric studies.

Labeling
On June 21, 2005, the Division and NitroMed, Inc. came up with a final draft package insert. Please refer to the Labeling section of the action package. Also included in the Labeling section of the action package are the original package insert and the proposed package insert submitted as part of their December 21, 2004 complete response.

DDMAC
Please refer to reviews in the action package in sections LNC Committee Reviews and Advertising.

Advisory Committee Meeting
An Advisory Committee Meeting took place on June 16, 2005

Project Manager's Summary
To my knowledge, there are no issues that might prevent action on this NDA.

Dianne C. Paraoan
Regulatory Health Project Manager

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

/s/

Dianne Paraoan
7/7/05 01:29:12 PM
CSO

19 Page(s) Withheld

____ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

29 Page(s) Withheld

____ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

NDA 20-727

No Division Director's Memo for the complete response submitted December 21, 2004

NDA 20-727

Proposed labeling submitted as part of their complete response submission dated December 21, 2004

✓ Transcript and Quick minutes

____Sponsor's Briefing Material

____ FDA'S Briefing Material

6 PAGES REMOVED. SEE THE ADVISORY COMMITTEE MEETING INFORMATION LOCATED ON THE FDA WEBSITE BELOW:

http://www.fda.gov/ohrms/dockets/ac/

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 20-727	Efficacy Supplement Type SE- N/A	Supplement Number N/A	
Drug: BiDil (isosorbide dinitrate and hydralazine HCl)		Applicant: NitroMed, Inc.	
RPM: Dianne Paraoan		HFD- 110	Phone # 301-594-5308

Application Type: () 505(b)(1) **(X)** 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** **(X)** Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): The reference listed drugs (RLD) for these drug products are: NDA 08-303 Apresoline (hydralazine HCl) NDA 12-093 Isordil (isosorbide dinitrate)

❖ Application Classifications:	
• Review priority	**(X)** Standard () Priority
• Chem class (NDAs only)	4
• Other (e.g., orphan, OTC)	N/A
❖ User Fee Goal Dates	June 23, 2005
❖ Special programs (indicate all that apply)	**(X)** None Subpart H () 21 CFR 314.510 (accelerated approval) () 21 CFR 314.520 (restricted distribution) () Fast Track () Rolling Review () CMA Pilot 1 () CMA Pilot 2
❖ User Fee Information	
• User Fee	() Paid UF ID number
• User Fee waiver	() Small business () Public health () Barrier-to-Innovation () Other (specify)
• User Fee exception	() Orphan designation () No-fee 505(b)(2) **(X)** Other No fee complete response to NA letter of July 2, 1997
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	() Yes **(X)** No
• This application is on the AIP	() Yes **(X)** No
• Exception for review (Center Director's memo)	N/A
• OC clearance for approval	N/A

❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(X) Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) (X) Verified 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	(X) N/A
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	(X) N/A (no paragraph IV certification) ( ) Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).* (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (3).* (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of	( ) Yes ( ) No ( ) Yes ( ) No ( ) Yes ( ) No

receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))). *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.* (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (5).* (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	( ) Yes ( ) No ( ) Yes ( ) No
• Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	( ) Yes (X) No
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	( ) Yes, Application #_____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	June 2, 2005 (PM)

General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	NA- July 2, 1997
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None (X) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter (X) Information Advisory
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	June 21, 2005
• Most recent applicant-proposed labeling	January 7, 2005
• Original applicant-proposed labeling	June 27, 1996 (original submission) December 21, 2004 (complete response)
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	DMETS: May 19, 2005 February 25, 2005 DDMAC: March 3, 2005 Labeling Mtgs: April 25, May 6 and 19, June 2, 8, 14, and 21, 2005
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	Yes
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	June 9, 2005
• Reviews	DMETS: May 19, 2005
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	Yes
❖ Memoranda and Telecons	Yes
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	November 30, 1995
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	Yes

❖ Advisory Committee Meeting	
• Date of Meeting	June 16, 2005
• 48-hour alert	Yes
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	May 6, 2005
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	Dr. Temple: June 21, 2005
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	April 15 and May 17, 2005 (June 23, 2005- replacement review of April 15 and May 17, 2005)
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	May 17, 2005
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	June 6, 2005
❖ Demographic Worksheet *(NME approvals only)*	N/A
❖ Statistical review(s) *(indicate date for each review)*	May 4, 10, and 18, 2005
❖ Biopharmaceutical review(s) *(indicate date for each review)*	April 15, 2005
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	May 17 and June 21, 2005
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	May 17, 2005
• Review & FONSI *(indicate date of review)*	August 28, 1996
• Review & Environmental Impact Statement *(indicate date of each review)*	May 17, 2005
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	N/A
❖ Facilities inspection (provide EER report)	Date completed: May 17, 2005 **(X)** Acceptable **( )** Withhold recommendation
❖ Methods validation	**( )** Completed **(X)** Requested **( )** Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	April 20 and June 20, 2005
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

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/s/

Dianne Paraoan
7/7/05 01:36:24 PM

Memorandum

To: File BiDil, NDA 20-727 (isosorbide dinitrate/hydralazine HCl)

From: Director, ODE1

Date: June 21, 2005

Subject: BiDil

I. Introduction

With the advisory committee meeting over, it seemed useful to summarize some critical issues, notably the strength of evidence supporting BiDil's overall effectiveness in the black population studied, the strength of evidence of an effect on survival and the evidence against an effect in the white population. This memo must, of course, be considered with the detached medical and statistical reviews.

II. Overall Strength of Evidence

The primary endpoint of A-HeFT represented relatively uncharted territory, combining death, hospitalization, and large changes on Minnesota Living with Heart failure Scale (referred to as a QOL scale, a point taken up later) in a single composite endpoint. Partly because the QOL value was not an "event", the composite did not use a time to event approach but counted and scored events as:

Death during the first 18 months (-3)
Hospitalization for CHF in 18 months (-1)
Change in QOL at 6 months

+≥10 units	(+2)
+>5 and <10	(+1)
<5	(0)
-≥5-<10	(-1)
-≥10	(-2)

The idea of giving different weights to components of a composite score is not new and has appeal but, to my best recollection, we have not seen this in formal submissions, at least not recently. Obviously, any weighting is highly

debatable but one could also argue that combining death, AMI (no matter how small) and urgent revascularization, a common composite endpoint, without any weighting is equally debatable. Fortunately, as will be described below, each endpoint component was itself statistically significant.

A problem arose from the early termination of the study because of the very stringent rules for missing data. Patients lost to follow up were to be given a score of (-3), lost to hospitalization status a score of (-1) and those without a 6-month QOL measure (-2). The first 2 were not major problems (vital status was available for all patients and hospitalization for most), but many patients had no 6 months QOL score because of the study termination and were given a (-2) score. The composite endpoint was significant at p=0.021 despite this but the QOL component was not significant because of the way non-completers were handled. Dr. Hung thinks the overall composite endpoint significance is over-conservative because of the (-2) given non-completers and describes the p-value for this composite as "<0.021".

In any case we have not only the single time point composite score but separate analyses of overall mortality, time to CHF hospitalization, time to death or CHF hospitalization (not a planned secondary endpoint, but a widely used one), all analyzed by both time to event procedures (COX regression). Results of the COX regressions and a pairwise comparison of days in hospital for CHF are shown below. Kaplan-Meier Curves are pictured in the stats review (p14) for death and hospitalization and in the sponsor's submission for the advisory committee (p83) for death or hospitalization:

Endpoints	Bidil N=518	Placebo N=532	HR	p-value
Composite	-0.16	-0.47		<0.021 (Hung)
Death	32 (6.2%)	54 (10.2%)	0.57 (0.37-0.89)	0.012
CHF Hosp'n	85 (16.4%)	130(24.4%)	0.61 (0.46-0.80)	< 0.001
Death or CHF Hosp	108 (20.8%)	158(29.7%)	0.63 (0.49-0.81)	< 0.001
Hosp days for CHF/pt	2.3	3.8		0.001

The QOL component of the primary endpoint standing alone was NS (MOR p 33), probably because of the way missing data were handled. More informative are the results over time (MOR p 37), showing very consistent advantages for BiDil at every 3 month visit except for 12 and 15 months (similar numerical difference, but fewer patients) with p<0.01 for an endpoint (last available measurement) evaluation.

An issue at the Advisory Committee meeting was whether the strength of evidence represented the "2 study equivalent," i.e., a p-value in the neighborhood of 0.001). My conclusion is that it does even without much support from V-HeFT I and II. Each of 3 correlated but independent endpoints shows nominal statistical significance, with hospitalization (a planned secondary endpoint) significant at $p<0.001$, together with death plus hospitalization (not specified but obvious) also at $p<0.001$). Properly analyzed, the QOL result is also significant at $p=0.01$.

III. Strength of Evidence of Survival Effect

The mortality fielding was the subject of a good deal of discussion, with Dr. Fleming identifying the "real" p-value as about 0.04. He did not think a mortality claim should appear in labeling. I do not agree. We do not usually expect a survival effect to be as statistically strong as other effects because there are generally fewer events and the importance of the event makes it ethically difficult to attain extreme p-values (i.e., studies tend to be stopped before extreme p-values are attained). Examples of this come from carvedilol post-MI and other sources. Second, I think the finding here is not marginal. As most of the mortality data were collected after the "interim look," I believe a doubling of the calculated p-value is excessive (2 completely independent, uncorrelated endpoint would, by Bonferroni adjustment, require doubling the nominal p-value. Here we clearly need a lesser correction, as the data involved in the final evaluation include data in the first evaluation. Moreover, the increased sample size was not based on mortality, raising the question of whether any correction is needed; Dr. Fleming said it did because mortality was correlated with the interim results, but this seems at least a matter for discussion. In any event, I believe the mortality finding is strengthened by hospitalization results as well as by the V-HeFT I and II results. It is also strengthened, as are the overall data, but a high degree of consistency in various subgroups

Baseline Characteristic	Mortality		First Hospitalization	
	Yes	No	Yes	No
All Patients	0.47	----	0.61	-----
Drugs				
ACEI	0.78	0.28	0.65	0.50
ARB	0.72	0.62	0.60	0.61
BB	0.66	0.46	0.60	0.64
CCB	1.07	0.50	0.71	0.59
Ald Antag	0.28	0.80	0.48	0.70
Other Diuretic	0.55	1.13	0.59	1.39
Digoxin	0.50	0.79	0.65	0.35
Etiology				
Ischemic	0.46	0.63	0.54	0.63
Hypertensive	0.50	0.61	0.56	0.64
History of Hypertension	0.49	1.32	0.65	0.40
Syst P > 125 @ BL	0.75	0.54	0.70	0.57
Male	0.79	------	0.60	------
Female	0.36	------	0.62	------
< 65	0.73	------	0.57	------
≥ 65	0.33	------	0.70	------

The results of V-HeFT I and II on mortality (in admittedly post-facto analyses) provide further support for the mortality finding in A-HeFT. First, the trials were primarily mortality studies, although other endpoints were considered. Second, in the black subset, results were quite strong, especially in V-HeFT I.

V-HeFT I	BiDil	Placebo	HR	p-value (log rank)
Overall	186 38.7%	276 44%	0.78 (0.58-1.04)	0.093
Black	49 30.6%	79 44.3%	0.53 (0.29-0.98)	0.04
White	136 41.9%	194 43.8%	0.88 (0.63-1.24)	0.47

V-HeFT II	BiDil	Enalapril	HR	p-value
Overall	401 38.2%	403 32.8%	1.23 (0.97-1.55)	0.083 (favoring E)
Black	109	106	1.01 (0.65-1.58)	p=0.96
White	282	292	1.39 (1.05-1.83)	p=0.02

V-HeFT I thus is a second finding of a survival advantage, admittedly weakened by the post-facto nature of the analysis, but very consistent with, and supportive, of A-HeFT. V-HeFT II was a study that actually was able to show a near significant advantage for enalapril over BiDil, nominally significant in whites. In the black subset, however, there is no suggestion of such a disadvantage. In this small subset, we obviously do not see documented non-inferiority (you'd want an upper bound of something like 1.25 to do that) but the study plainly shows no suggestion of inferiority to enalapril in the black subset.

IV. Effect in White Population

Two Advisory Committee members and several audience members urged approval of BiDil for all people with CHF, not just self-identified blacks. As indicated above, in two studies (V-HeFT I and II)that strongly suggested effectiveness for blacks (evidence of assay sensitivity), there was no hint at all of an effect in the overall white population. This is clearest in V-HeFT I, where the small black population showed a survival effect but the larger white population gave almost no hint of benefit. Similarly in V-HeFT II, BiDil in whites was about as inferior to enalapril as one would expect a placebo to be. There are thus 2 randomized trials, each with evidence of assay sensitivity (i.e., the ability to detect mortality effects), that show no reasonable evidence of an effect in blacks, but real hint of activity in whites. Labeling BiDil for a white population would fly in the face of evidence.

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/s/

Robert Temple
7/8/05 07:11:54 PM
MEDICAL OFFICER

18 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

MEMORANDUM TO FILE

DATE: June 24, 2005

TO: NDA 20-727

FROM: Dianne Paraoan
Regulatory Health Project Manager, HFD-110

SUBJECT: **Addendum to appendix B of the filing review**
NDA 20-727, BiDil® (isosorbide dinitrate and hydralazine hydrochloride) Tablets, 20mg/37.5mg

1. Reference is made to the June 20, 2005 review- Appendix B to NDA Regulatory Filing Review Questions for 505(b)(2) Applications.

2. Question #11 "Which of the following patent certifications does the application contain?" stating that the patent information has not been submitted to the FDA is incorrect.

3. The correct response to Question #11 is 21CFR314.50(i)(1)(ii): No relevant patents.

4. The sponsor, NitroMed, Inc. stated this in their June 23, 2005 submission.

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/s/

Dianne Paraoan
6/24/05 10:23:42 AM
CSO

MEMORANDUM OF TELECON

DATE: June 2, 2005

APPLICATION NUMBER: NDA 20-727 BiDil (isosorbide dinitrate/ hydralazine HCl)

BETWEEN:	NitroMed, Inc.
Name:	Manuel Worcel, Chief Medical Officer, NitroMed
	Mike Sabolinski, Senior VP, Clinical Research and Regulatory Affairs, NitroMed
	Mike Loberg, Chief Executive Officer, NitroMed
	Carol Gloff, Regulatory Consultant to NitroMed
	[ ] FoxKiser
	[ ] FoxKiser
AND	Division of Cardio-Renal Drug Products, HFD-110
Name:	Norman Stockbridge, M.D., Ph.D., Acting Division Director
	Salma Lemtouni, M.D., M.P.H., Medical Officer
	James Hung, Ph.D., Team Leader, Statistician, HFD-710
	Kris Raman, Chemist, Ph.D., HFD-
	Peter Hinderling, M.D., Clinical Pharmacologist, HFD-860
	Lydia Velazquez, Pharm.D., Clinical Pharmacologist, HFD-860
	Dianne Paraoan, Regulatory Project Manager

PURPOSE: NitroMed, Inc. requested this teleconference in preparation of the Cardio-Renal Advisory Committee (CRAC) meeting.

DISCUSSION:

Advisory Committee Meeting

NitroMed, Inc. informed the Division that they have received the Division's background package for the CRAC. They noted that the questions in the package are in draft form and inquired when the final version will be available to them. Dr. Stockbridge stated that they have already been modified by Dr. Temple and that they may not get the final questions until 1-2 days before the meeting.

The sponsor stated that they have had mock trial runs of their presentation and wanted to ensure that they addressed all concerns appropriately. The Division informed the sponsor that the Division, as commonly done, will not be making a presentation. Dr. Stockbridge suggested that the sponsor not make their presentation any longer than is allowed as there will likely be interruptions that will make their presentation even longer.

NitroMed, Inc. asked the Division about the role of V-HeFT I and V-HeFT II during the CRAC. Dr. Stockbridge encouraged the sponsor to focus on the A-HeFT trial and lay out a basis as to what brought them to that trial.

Dr. Stockbridge informed the sponsor that an ethicist from NIH, Dr. Wang, will be an additional member of the committee.

Labeling

NitroMed, Inc. asked the Division when it would be possible to have a face to face labeling discussion. Dr. Stockbridge assured the sponsor that the Division is working on the label and will have a draft for

them to review before the weekend. Dr. Stockbridge further stated that he will discuss the possibility of a meeting with Dr. Temple.

Pending CMC issues
Dr. Stockbridge asked the sponsor when they plan on addressing the pending CMC issues given to them in a discipline review letter on May 11, 2005. He informed them of the urgency of having these issues resolved before an action can take place. NitroMed, Inc. assured the Division that they are diligently working on addressing the CMC issues.

PLANS:

1. The CRAC meeting is as scheduled for June 16, 2005.
2. The sponsor will provide the Division their response to the CMC issues.
3. The Division will provide the questions regarding the CRAC as soon as possible.
4. The Division will provide the sponsor the draft package insert by Friday.

Norman Stockbridge, M.D., Ph.D.
Acting Director
Division of Cardio-Renal Drug Products

Draft: 6/605 Final: 6/8/05
RD:
Stockbridge: 6/7/05
Lemtouni: 6/7/05
Hung: 6/7/05
Hinderling: 6/7/05
Velazquez: 6/6/05

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/s/

Norman Stockbridge
6/8/05 08:16:03 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-727

5-25-05

NitroMed, Inc.
Attention: Michael Sabolinski, M.D.
125 Spring Street
Lexington, MA 02421

Dear Dr. Sabolinski:

Please refer to your submission dated May 6, 2005, requesting a waiver for pediatric studies for BiDil® (isosorbide dinitrate/hydralazine HCl) Tablets.

We also refer to your December 21, 2004 resubmission and our February 3, 2005 letter initially granting you a deferral of pediatric studies for the treatment of heart failure in pediatric patients ages 6 to 16 years of age and a waiver of pediatric studies for the treatment of heart failure in pediatric patients ages < 1 month to < 6 years of age.

We have reviewed the submission and now agree that a waiver is justified for BiDil® (isosorbide dinitrate/hydralazine HCl) Tablets for the treatment of heart failure in black patients for the entire pediatric population because:

1. There is considerable doubt that the heart failure in children is close enough to the heart failure in adults to make such as study likely to succeed.

2. Necessary studies are impossible or highly impractical because the number of such patients is so small.

Accordingly, at this time, a waiver for pediatric studies for your application is granted under section 2 of the Pediatric Research Equity Act.

If you have questions, please contact

Ms. Dianne Paraoan
Regulatory Project Manager
301-594-5308

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Acting Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Norman Stockbridge
5/25/05 09:37:20 AM

5-13-05

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: April 12, 2005	**DESIRED COMPLETION DATE:** 5/16/2005 **PDUFA DATE:** 6/23/2005	**ODS CONSULT #:** 04-0266-1

TO: Norman Stockbridge
Acting Director, Division of Cardio-Renal Drug Products
HFD-110

THROUGH: Dianne Paraoan
Project Manager
HFD-110

PRODUCT NAME: **BiDil** (Hydralazine Hydrochloride and Isosorbide Dinitrate Tablets) 37.5 mg/20 mg **NDA: 20-727**	**SPONSOR:** NitroMed, Inc.

SAFETY EVALUATOR: Laura Pincock, Pharm.D.

RECOMMENDATIONS:

DMETS recommends implementation of the container labels and insert labeling revisions outlined in Section II of this review in order to minimize potential user error.

Denise P. Toyer, Pharm.D.
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Carol Holquist, R.Ph.
Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research

LABEL AND LABELING REVIEW

DATE OF REVIEW: April 26, 2005

NDA # 20-727

NAME OF DRUG: **BiDil**
(Hydralazine Hydrochloride and Isosorbide Dinitrate Tablets)
37.5 mg/20 mg

NDA HOLDER: NitroMed, Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Cardiorenal Drug Products (HFD-110) to review and comment on the container labels and insert labeling of BiDil which were submitted on April 5, 2005 and April 12, 2005. DMETS had previously reviewed the proprietary name BiDil in Consult 04-0266 dated February 25, 2005. DMETS objected to the proposed proprietary name, BiDil, because the name may be misleading to practitioners and lead them to believe that the product is dosed twice daily when it is actually dosed three times a day. Despite these concerns, the Division of Cardio-Renal Drug Products made the decision to accept the tradename BiDil.

PRODUCT INFORMATION

BiDil is a tablet containing Hydralazine Hydrochloride and Isosorbide Dinitrate, two vasodilator drug products. BiDil is proposed to be indicated for the treatment of chronic congestive heart failure as an adjunct to standard therapy in black patients who are intolerant or have a contraindication to angiotensin-converting enzyme (ACE) inhibitors. BiDil will be available as 37.5 mg Hydralazine Hydrochloride and 20 mg Isosorbide Dinitrate in a fixed-dose combination tablet. Treatment with BiDil is initiated at one tablet three times daily. BiDil may be titrated to a maximum of two tablets three times a day or to the maximum tolerated dose.

II. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In the review of the BiDil container labels and insert labeling, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which may minimize potential user error.

A. GENERAL COMMENTS

'BiDil' and 'BiDil 20' are used interchangeably throughout the container labels and package insert labeling. The proposed proprietary name is BiDil and not BiDil 20. It is misleading to highlight only one ingredient when the drug product actually contains two active ingredients (21 CFR 201.6). Delete the numeric modifier and refer to the tradename as 'BiDil' consistently throughout the container labels and package insert labeling.

B. CONTAINER LABELS [Trade (42 tablets and 180 tablets) and Sample (12 Tablets)]

1. See General Comment A.

2. The presentation of the established name 'isosorbide dinitrate 20 mg/hydralazine HCl 37.5 mg' is compacted and difficult to read. It is important that the practitioner be able to readily distinguish between the different combination of potencies of this product. To meet both the regulatory requirements of the established name and the need to identify the intended product without undue repetition, we suggest the following as the established name:

   Isosorbide Dinitrate **20 mg**
   and
   Hydralazine Hydrochloride **37.5 mg**

   Please note that the milligram amounts of hydralazine and isosorbide would appear in colored boxes so as not to be part of the established name, yet be positioned such that the drug is easily identifiable to the appropriate strength. If the colored box format is not possible, we would accept the following format:

   Isosorbide Dinitrate and Hydralazine Hydrochloride Tablets
   20 mg/37.5 mg

3. The current presentation of the net quantity (180 Tablets, 42 Tablets, or 12 Tablets) is more prominent than the drug strengths. The drug strengths should be featured more prominently than the net quantity statement. Revise accordingly.

4. Revise the font and layout of the text on the labels so that it is easier to read. The orange and white font on the red label makes the label text difficult to read. Revise the colors so the text is more legible. Additionally, the font on the [ ] count bottles are too small to read. Revise accordingly.

5. Since the bottles are unit-of-use, ensure they have child-resistant caps (CRC) to be compliant with the Poison Prevention Act.

6. Increase the prominence of the statement, "SAMPLE NOT FOR SALE".

C. PACKAGE INSERT

1. See General Comment A.

2. The dosage recommendations state that the 'Treatment with BiDil should be initiated at a dose of one BiDil tablet, three times a day. BiDil may be titrated to a maximum of two BiDil tablets, three times a day or to the maximum tolerated dose.' DMETS is concerned that the last part of this recommendation 'or to the maximum tolerated dose' implies that if a patient can take tolerate more, than they can take more than the recommended maximum amount. As currently stated, this recommendation implies there is no ceiling to the dose. Please clarify or state the exact maximum dose allowable for the patient.

III. DMETS RECOMMENDATIONS:

DMETS recommends implementation of the labeling revisions outlined in Section II of this review.

DMETS 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 Scott Dallas, project manager, at 301-827-7849.

Laura L. Pincock, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Linda Kim-Jung, Pharm.D.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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/s/

Laura Pincock
5/13/05 03:48:18 PM
DRUG SAFETY OFFICE REVIEWER

Linda Kim-Jung
5/17/05 10:01:55 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
5/18/05 11:46:10 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
5/19/05 04:07:37 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM OF TELECON

DATE: May 13, 2005

APPLICATION NUMBER: NDA 20-727 BiDil (isosorbide dinitrate/ hydralazine HCl)

BETWEEN:		NitroMed, Inc.
	Name:	Manuel Worcel, Chief Medical Officer, NitroMed
		Mike Sabolinski, Senior VP, Clinical Research and Regulatory Affairs, NitroMed
		Mike Loberg, Chief Executive Officer, NitroMed
		Carol Gloff, Regulatory Consultant to NitroMed
AND		Division of Cardio-Renal Drug Products, HFD-110
	Name:	Norman Stockbridge, M.D., Ph.D., Acting Division Director, HFD-110
		Edward Fromm, Chief, Project Management Staff, HFD-110
		Dianne Paraoan, Regulatory Project Manager, HFD-110

PURPOSE: NitroMed, Inc. requested this teleconference after receiving the draft proposed list of questions that will be presented at the Cardio-Renal Advisory Committee (CRAC) meeting.

DISCUSSION:

NitroMed, Inc. informed the Division that they are currently working on the briefing document, but will not be able to submit their briefing document as requested to meet the Office of Advisors and Consultants' (ACS) timeline. Dr. Stockbridge informed them that they will need to discuss this with the ACS because they have their own guidelines and review processes. It seems feasible that they could submit the bulk of the material today and perhaps negotiate an appendix for a later submission. The sponsor stated that hey have already notified the ACS and have spoken to Dornette Spell-Lesane. The sponsor will continue discussions with the ACS.

NitroMed, Inc. added that after reviewing the draft questions, they want to include additional analyses in their briefing document. They anticipate submitting the additional analyses to the briefing document and then following up with an amendment to their application. Dr. Stockbridge stated that it is acceptable to submit an amendment.

The sponsor argued one of the draft questions regarding the effect on hospitalization. They stated that the information was not provided in the NDA, but because they do see a significant difference, will include it as discussed above in the briefing documents and as an amendment. Dr. Stockbridge suggested that they provide an analysis of total days of hospitalization adjusted for total days at risk. NitroMed agreed to provide this analysis.

The sponsor then asked for clarification to the question regarding blood pressure. Subjects randomized to BiDil had lower blood pressure than those randomized to placebo. Dr. Stockbridge stated that they should provide an explanation about the blood pressure difference during the trial, not at baseline. He added that even if there is an effect on blood pressure with the drug during the trial, it would in no way negate the apparent benefit on outcomes in the African American population.

Regarding the package insert, NitroMed, Inc. asked Dr. Stockbridge when they can anticipate labeling discussions. Dr. Stockbridge informed them that we are currently working on the labeling and should have proposed labeling for them by the end of next week.

PLANS:

1. NitroMed, Inc. should contact the ACS to inform them that they can not meet established timeline to submit their briefing package and to negotiate a new completion date.

Norman Stockbridge, M.D., Ph.D.
Acting Director
Division of Cardio-Renal Drug Products

Draft: 5/13/05 Final: 5/19/05
RD:
Stockbridge: 5/18/05
Fromm: ef 5/16/05

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/s/

Norman Stockbridge
5/19/05 07:49:52 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

5-11-05

NDA 20-727

DISCIPLINE REVIEW LETTER

NitroMed, Inc.
Attention: Michael Sabolinski, M.D.
125 Spring Street
Lexington, MA 02421

Dear Dr. Sabolinski:

Please refer to your December 21, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for BiDil (isosorbide dinitrate and hydralazine HCl) Tablets.

We also refer to your submission dated April 27, 2005.

Our review of the Chemistry, Manufacturing and Controls section of your submission is complete, and we have identified the following deficiencies:

Drug Substance

1. Please clarify what is meant by [ ] and provide justification why a single point specification is adequate for isosorbide dinitrate.
2. Please refer to specification for 'any impurity' NMT [ ] established by [ ] [ ] for Hydralazine HCl, USP. Since the limit of [ ] over the ICH identification and qualification threshold, any impurity at these levels need to be identified and qualified or alternatively the specification should be revised to "any unspecified impurities NMT [ ]
3. Please provide a rationale for not including [ ] in the drug substance regulatory specifications for hydralazine HCl and in the batch analysis, although this is included in the Certificate of Analysis provided by the vendor (Appendix C of submission).

Drug Product

1. HPLC retention time alone is not adequate for identification of the drug substance in the drug product specifications according to the ICH Q6A Guidelines. Additional identification tests such as HPLC/UV diode array, HPLC/MS, or IR should be included in the drug product specifications.
2. Please include [ ] specification in the drug product specifications or provide rationale for not including it as part of specifications.
3. We consider the [ ] a degradant/impurity because its content increases on storage, which shouldn't be the case if this was just an artifact of sample handling. The proposed release and shelf life specification for [ ] is 2 – 3 times the qualification threshold. Since the proposed limit is over ICH qualification threshold of [ ] this [ ] should be qualified.
4. The release specification for individual unspecified impurities established as 'Report any individual peak [ ], by area' is not acceptable. Please revise this to "any unspecified impurities/degradants NMT [ ] in accordance with ICH Q3B(R).
5. Please clarify why 1-Phthalazinone which is a potential impurity/degradant in the drug product (refer to Section 4.3.10.3.5 second paragraph, page 101) is not listed in the drug product specifications.
6. Please refer to the batch data on page 104, Volume 1, which does not conform to the proposed drug product specifications with respect to specified impurities/degradants. Please explain why specified impurities/degradants were not reported in accordance with the proposed drug product specifications.

7. Please explain why other packaging sizes, [ ] have been used under the current stability protocol when they are not be marketed.
8. Please note that for some drug product batches on stability there was an increase in the level of unknown individual impurities above the ICH Q3B(R) identification and qualification threshold levels based on the maximum amount of drug administered per day. These impurities should be identified and qualified.
9. Please provide stability data for at least three batches of each packaging configuration, in order to support the requested shelf life for the — count tablet sample size, — count tablet sample size, and 180-count tablet commercial packaging configurations.
10. You have proposed to market BiDil® 20 Tablets in one packaging configuration, 180-count tablets in 100 cc HDPE bottles. However, Schwarz Pharma's stability commitment letter (Volume 2, Appendix P) states that "the first three production batches packaged in the smallest and largest package configurations will be placed on concurrent stability". Please clarify the configurations of these additional packages. We also remind you that at least three marketed batches of 180-count need to put on stability.
11. Please use the compendial names for the inactive ingredients lactose, cellulose, and silicon dioxide in the description section of 'Package Insert'; for the Opadry orange coating, all the ingredients in the coating formulation should be listed.
12. The Division recommends that the number '20' used after the trade name BiDil® should be removed because this adds more confusion to both the practitioner and the patients.

In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, please call
Dianne C. Paraoan
Regulatory Health Project Manager
(301) 594-5308

Sincerely,

See appended page for electronic signature

Norman Stockbridge, M.D., Ph.D.
Acting Division Director
Division of Cardio-Renal Drug Products, HFD-110
Office of Drug Evaluations I
Center for Drug Evaluation and Research

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/s/

Norman Stockbridge
5/11/05 01:43:15 PM

MEMORANDUM OF TELECON

DATE: May 6, 2005

APPLICATION NUMBER: NDA 20-727 BiDil (isosorbide dinitrate/ hydralazine HCl)

BETWEEN: NitroMed, Inc.

Name: Manuel Worcel, Chief Medical Officer, NitroMed
Mike Sabolinski, Senior VP, Clinical Research and Regulatory Affairs, NitroMed
Mike Loberg, Chief Executive Officer, NitroMed
Carol Gloff, Regulatory Consultant to NitroMed
[ ] FoxKiser
[ ] FoxKiser
[ ] FoxKiser

AND
Division of Cardio-Renal Drug Products, HFD-110

Name: Norman Stockbridge, M.D., Ph.D., Acting Division Director, HFD-110
Abraham Karkowsky, M.D., Acting Deputy Director, HFD-110
Salma Lemtouni, M.D., M.P.H. Medical Officer, HFD-110
Peter Hinderling, M.D., Clinical Pharmacologist, HFD-860
Lydia Velazquez, Pharm.D., Clinical Pharmacologist, HFD-860
Jim Hung, Ph.D., Team Leader, Statistics, HFD-710
Dianne Paraoan, Regulatory Project Manager, HFD-110

PURPOSE: NitroMed, Inc. requested this teleconference to assist with the briefing document and presentation of their application at the Cardio-Renal Advisory Committee (CRAC) meeting scheduled on June 16, 2005

DISCUSSION:

NitroMed, Inc. informed the Division that they intend on submitting the briefing document on time as described in their timeline. They are aware that the briefing document will be available publicly.

The sponsor wanted the Division to agree on the indication prior to May 13, 2005, the due date of the briefing document, to ensure that their briefing document includes information to support their claim. NitroMed, Inc. plans to provide data to support the claim indicated in their complete response dated December 21, 2004. Dr. Stockbridge recommended that the sponsor lay out supportable claims, and not worry about what was submitted in the label. After much discussion, Dr. Stockbridge assured the sponsor that labeling discussion will be started before the CRAC, but that we will not be able to discuss the claim before the briefing document is due to the Office of Advisors and Consultants (ACS). Nonetheless, the sponsor was encouraged to include their best case to support their claim in their briefing document.

NitroMed, Inc. referenced the April 7, 2005 teleconference in which we informed them that their application will be going to the CRAC. During the teleconference, we discussed statistical issues regarding the difference in the hazard ratios computed pre- and post-interim analysis for sample size re-estimation and the absence of detailed concomitant medication data post-baseline. Since then, the sponsor has submitted several responses. NitroMed, Inc. wanted to know if their response was adequate. After some internal discussion, Dr. Stockbridge informed the sponsor that the description results are part of the statistical review and that we are less concerned about the results than we were when the issue was first

raised. Because the CRAC will have a copy of the reviews, Dr. Stockbridge encouraged the sponsor to be prepared to discuss this issue.

Dr. Stockbridge informed the sponsor that if any additional issues arise, we will notify them immediately. Furthermore, if additional information needs to be included in their briefing document because of a new issue, we will discuss the need for an addendum with the ACS.

PLANS:

1. NDA 20-727 will go to the CRAC on June 16, 2005. The sponsor should contact the ACS for any questions about the CRAC, but are welcomed to contact the Division.
2. NitroMed, Inc. will continue meeting the timeline established by the ACS.
3. The Division will notify NitroMed, Inc. if any additional issues affecting the CRAC arise.

Norman Stockbridge, M.D., Ph.D.
Acting Director
Division of Cardio-Renal Drug Products

Draft: 5/11/05 Final: 5/12/05
RD:
Stockbridge: 5/12/05
Karkowsky:5/12/05
Lemtouni: 5/11/05
Hinderling:5-11-05
Hung: 5/11/2005

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/s/

Norman Stockbridge
5/12/05 12:14:59 PM

MEMORANDUM OF TELECON

DATE: May 2, 2005

APPLICATION NUMBER: NDA 20-727 BiDil (isosorbide dinitrate/ hydralazine HCl)

BETWEEN: NitroMed, Inc.

Name: Manuel Worcel, Chief Medical Officer, NitroMed
Mike Sabolinski, Senior VP, Clinical Research and Regulatory Affairs, NitroMed
Mike Loberg, Chief Executive Officer, NitroMed
Carol Gloff, Regulatory Consultant to NitroMed
[ ] FoxKiser

AND Division of Cardio-Renal Drug Products, HFD-110

Name: Norman Stockbridge, M.D., Ph.D., Acting Division Director, HFD-110
Edward Fromm, Chief, Project Management Staff, HFD-110
Dianne Paraoan, Regulatory Project Manager, HFD-110

Office of Advisors and Consultants
Dornette Spell-Lasane, HFD-021
Jayne Peterson, HFD-021
Cathy Groupe, HFD-021

PURPOSE: The sponsor requested this teleconference to discuss the posting of their application being brought to the Cardio-Renal Advisory Committee (CRAC) on June 16, 2005 as seen on the FDA website.

DISCUSSION:

NitroMed, Inc. asked the Division what steps they will need to do to move forward with respect to the CRAC. Last week, the sponsor submitted a letter to the Division requesting that their application not go before the CRAC. Dr. Stockbridge informed the sponsor that he forwarded their letter to both Drs. Temple and Throckmorton. Despite the letter, Drs. Temple and Throckmorton expressed their interest in having BiDil go to the CRAC.

Dr. Stockbridge discussed the two issues of concern for their application to go before the CRAC.
1. Race- based therapy
2. The difference in trial outcome when comparing the cohort enrolled prior to and after.

Both issues were discussed at a previous teleconference with the sponsor on March 8, 2005. The sponsor addressed the second area of concern in the April 15 and 22, 2005 submission to Dr. Hung and stated that there are no pending issues.

The sponsor expressed concerns that although the development of a drug for a specific culture or race is an important issue, they believe that they are not the right people, nor is the CRAC the right media for that discussion. Dr. Stockbridge suggested that NitroMed, Inc. focus on presenting the developmental program for the drug, showing how they came to design the A-HeFT trial. There is no need to address race in medicine.

Dr. Stockbridge informed NitroMed, Inc. that if they would like, they can discuss their concerns about the CRAC with Dr. Temple. NitroMed, Inc. will contact Ms. Paraoan to make arrangements.

NitroMed, Inc. informed the Division that they have sought guidance from Dr. Milton Packer and wanted confirmation from the Division that this is acceptable. Dr. Stockbridge agreed that it is acceptable to consult Dr. Packer for their preparation for the CRAC and their labeling. Ms. Peterson added that because he is a Special Government Employee (SGE), Dr. Packer will need to complete paperwork. NitroMed, Inc. stated that they will make the necessary arrangements and will contact the Office of Advisors and Consultants.

Again, NitroMed, Inc. inquired as to when labeling discussions will begin, asking that the package insert be finalized prior to the CRAC. Dr. Stockbridge assured the sponsor that once we meet internally to discuss labeling, we will schedule future meetings with them. He added that because parts of the package insert may be discussed with the CRAC, we should not negotiate a final label beforehand. NitroMed, Inc. informed the Division that they are internally working on the package insert. Dr. Stockbridge encouraged the sponsor to submit their amendment at their convenience. NitroMed, Inc. stated that they will submit their revised label by the end of next week.

PLANS:

1. NDA 20-727 will go to the CRAC on June 16, 2005. The sponsor should contact the Office of Advisors and Consultants for any questions about the CRAC, but are welcomed to contact the Division.
2. If desired, Ms. Carol Gloff will contact Ms. Paraoan to set up a meeting with Dr. Temple to discuss the possibility of not going to the CRAC.
3. NitroMed, Inc. will contact the Office of Advisors and Consultants to complete the necessary paperwork so that Dr. Milton Packer can be involved in the discussions with their application.
4. NitroMed, Inc. will submit their revised label by the end of next week.

Norman Stockbridge, M.D., Ph.D.
Acting Director
Division of Cardio-Renal Drug Products

Draft: 5/9/05 Final: 5/11/05
RD:
Stockbridge: 5/11/05
Fromm:5/10/05

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/s/

Norman Stockbridge
5/11/05 01:48:41 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

APR 2 1 2005

Food and Drug Administration
Rockville MD 20857

Michael L. Sabolinski, M.D.
Senior Vice President
Clinical Development and Regulatory Affairs
NitroMed, Inc.
125 Spring Street
Lexington, MA 02421

RE: Request for Refund of Fiscal Year 2005 Application Fee for a Resubmission to NDA 20-727, BiDil Tablets

Dear Dr. Sabolinski:

This responds to your February 17, 2005, letter requesting a refund of an additional application fee paid under the user fee provisions of the Federal Food, Drug, and Cosmetic Act (the Act)[1] for a resubmission to new drug application (NDA) 20-727, BiDil (isosorbide dinitrate and hydralazine hydrochloride) Tablets. For the reasons described below, the Food and Drug Administration (FDA) will refund the additional application fee paid by NitroMed, Inc. (NitroMed), for NDA 20-727, BiDil Tablets.

I. NitroMed's Request

In your request for a refund you state that NitroMed paid $672,000 on December 23, 2004,[2] for NitroMed's December 22, 2004, amendment to NDA 20-727. You state that at the time the user fee was paid, it was unclear whether your December 22, 2004, submission would be assigned a new NDA number, or whether it would be treated as a complete response to the July 2, 1997, FDA Not Approvable letter for NDA 20-727. You referenced a February 3, 2005, letter from Mr. Edward Fromm, Chief, Project Management Staff, FDA's Division of Cardio-Renal Drug Products (DCRDP), which you believe determined that your December 22, 2004, submission to NDA 20-727 was considered a complete, class 2 response to the FDA's July 2, 1997, Not Approvable letter. Therefore, you believe that NitroMed is eligible for a refund of the additional fee, because a fee is not necessary for a resubmission.

II. Background Information for NDA 20-727, BiDil Tablets

DCRDP received NitroMed's submission dated December 21, 2004, on December 23, 2004.[3] On February 3, 2005, DCRDP sent NitroMed an acknowledgment letter

[1] Sections 735 and 736 of the Act (21 U.S.C. 379(g) and 379(h)).
[2] User fee identification number (UFID #) 4910.
[3] You refer to the submission as your December 22, 2004, amendment. According to FDA records, the submission was dated December 21, 2004; therefore, we will refer to this submission for the rest of this letter as your December 21, 2004, submission.

indicating that the Division considered your December 21, 2004, submission a complete class 2 response[4] to FDA's July 2, 1997, letter. Your resubmission proposed that BiDil be indicated for the treatment of congestive heart failure as an adjunct to standard therapy in black patients who are intolerant or have a contraindication to angiotensin-converting enzyme (ACE) inhibitors. In addition, you claim BiDil improves survival in black patients with chronic congestive heart failure. The proposed labeling also states that clinical trials have demonstrated safety but have not conclusively demonstrated efficacy in non-black patients. The labeling, as submitted in the original application, states that BiDil is indicated for the treatment of chronic congestive heart failure as an adjunct to standard therapy (digitalis glycosides and diuretics) in patients who are intolerant or have a contraindication to ACE inhibitors. Finally, the original labeling states that BiDil improves survival and exercise tolerance in patients with chronic congestive heart failure.

III. Criteria for Assessment of Application Fees

Section 736(a)(1)(A) of the Act states that a human drug application that requires clinical data for approval is subject to a fee. Certain human drug applications are excepted from user fees under section 736(a)(1)(C) of the Act as follows:

> If a human drug application or supplement was submitted by a person that paid the fee for such application or supplement, was accepted for filing, and was not approved or was withdrawn (without a waiver), the submission of a human drug application or a supplement for the same product by the same person (or the person's licensee, assignee, or successor) shall not be subject to a fee under subparagraph (A).

According to FDA's guidance for industry on *Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees* (December 2004),[5] after initial submission, a pending application should not be amended to include a new indication or claim. It states:

> After initial submission, a pending original or supplemental application should not be amended to add a new indication or claim. Previously submitted indications or claims can be modified by, for example, reanalyses of previously submitted data or, in rare instances, supplementary clinical data. Such amendments could result in subsequent adjustments to the user fee review clock. Submitting new clinical or in vitro data to support a new claim(s) to an already submitted application during the review of that application is not recommended. Such a submission would be considered developing the product on the review clock and is contrary to the spirit and intent of the Act.

[4] Complete responses to action letters are also known as resubmissions.
[5] Available on the Internet at www.fda.gov/cder/pdufa/default.htm under Guidances.

IV. Evaluation of NitroMed's Request

We have reviewed our files and consulted DCRDP. According to DCRDP, the "new" indication proposed in the December 21, 2004, submission constitutes a change that can be considered a subset of the indication that was in the labeling in the original application. In other words, the December 21, 2004, submission included an indication modified by supplementary clinical data. As such, the submission was not considered to be a submission of new clinical data to support a new claim to an already submitted application. Therefore, a new application was not necessary. Because NitroMed's December 21, 2004, submission is considered to be a complete response to FDA's July 2, 1997, Not Approvable letter and not a new application, a new NDA application number is not required. Further, because (1) the fee was previously paid for this human drug application, (2) the application was filed and not approved or withdrawn (without a waiver), and (3) it was considered the same product by the successor,[6] your submission is not subject to a new fee. Therefore, your refund request is granted.

We have confirmed that FDA received the resubmission of NDA 20-727 on December 23, 2004. FDA was notified of receipt of NitroMed's application fee of $672,000 for the December 21, 2004, submission to NDA 20-727 on December 28, 2004. We have asked the Office of Financial Management (OFM) to refund the additional $672,000 application fee paid by NitroMed. If you do not receive the refund within 30 days of this letter, please contact Pothen (Sunny) Joseph, OFM, at 301-827-5086.

If you have any further questions regarding this matter or other user fee questions, please contact Beverly Friedman or Michael Jones at 301-594-2041.

Sincerely,

Jane A. Axelrad

Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

[6] The application was originally submitted and paid for by Medco. NitroMed acquired the application prior to your December 28, 2004, payment.

bcc:

M. Jones, HFD-5
NitroMed User Fee File, HFD-5
Chron File, HFD-5
B. Friedman, HFD-7
T. Schwemer, HFD-7
E.Fromm, HFD-110
C. Vincent, HFM-110
F. Claunts, HF-20
W.Collinson/K.Boyd HFA-100
P. Joseph/ HFA-120 (Refund Pending)
D. Hinton/E.Fromm, HFD-110
T. Forfa, HFV-3
D. Newkirk HFV-100

MJones 4.20.2005

J\USERFEE\LETTERS\NitroMed feb 05 bidil app refund v5.doc

Drafted: G. Davis 03/28/05
Revised: M. Jones 3/31/2005
Comments: B.Friedman 4/4/2005
Revised: M.Jones 4/5/2005
Edited: S.O'Malley 4/14/2005
Revised: M.Jones 4/15/2005
Concur: E.Fromm 4/15/2005
Typo's corrected: M.Jones 4/20/2005

MEMORANDUM OF TELECON

DATE: April 7, 2005

APPLICATION NUMBER: NDA 20-727 BiDil (isosorbide dinitrate/ hydralazine HCl)

BETWEEN: NitroMed, Inc.

Name: Manuel Worcel, Chief Medical Officer, NitroMed
Mike Sabolinski, Senior VP, Clinical Research and Regulatory Affairs, NitroMed
Mike Loberg, Chief Executive Officer, NitroMed
Carol Gloff, Regulatory Consultant to NitroMed
[redacted] FoxKiser
[redacted] FoxKiser
[redacted] FoxKiser

AND Division of Cardio-Renal Drug Products, HFD-110

Name: Norman Stockbridge, M.D., Ph.D., Acting Division Director, HFD-110
Abraham Karkowsky, M.D., Acting Deputy Director, HFD-110
Salma Lemtouni, M.D., Medical Officer, HFD-110
Peter Hinderling, Ph.D., Clinical Pharmacologist, HFD-860
Jim Hung, Ph.D., Team Leader, Statistics, HFD-710
Edward Fromm, Chief, Project Management Staff, HFD-110
Dianne Paraoan, Regulatory Project Manager, HFD-110

PURPOSE: The Division requested this teleconference with the sponsor to inform them that we will be bringing their application to the Cardio-Renal Advisory Committee (CRAC) on June 16, 2005.

DISCUSSION:

Advisory Committee Meeting

After introductions, Dr. Stockbridge informed the sponsor that because of the political ramifications targeting one racial group and public interest of BiDil, both Drs. Throckmorton and Temple requested that this application be put on the June agenda for the Cardio-Renal Advisory Committee (CRAC) meeting. He added that there is no controversy within the Division about the race issue and that they should be able to easily walk through the clinical development of the product.

NitroMed, Inc. is concerned that the meeting may lead to them having to address the broader issue; race in medicine. Dr. Stockbridge assured the sponsor that is not the intent and that we want to stay focused on the drug. The sponsor asked whether or not it would be possible to work on the labeling in advance of the CRAC meeting and possibly to get an action before the CRAC meeting. Dr. Stockbridge stated that although the meeting date and the goal date are a week apart, this would not be possible. The sponsor wanted to discuss the labeling today, but Dr. Stockbridge informed the sponsor that it is premature to talk about labeling now, but we can discuss the labeling once all the reviews have been completed and all the pieces on our side are together.

The sponsor asked about special government employees (SGEs). Dr. Stockbridge does not anticipate using SGEs. Next, the sponsor asked about the FR Notice and when we anticipate it being posted. The Office of Advisors and Consultants will inform NitroMed, Inc. before the FR Notice will be posted. We briefly discussed the timeline of when reviews and packages are due. The sponsor requested that we have

a teleconference before they submit their package before the meeting. Dr. Stockbridge agreed that this would be possible.

Because NitroMed, Inc. does not believe their application should go before the CRAC, they asked what they can do to get the Division and Office to reconsider its decision. Dr. Stockbridge informed the sponsor that they can write a letter to Drs. Temple and Throckmorton stating that they will go to the CRAC if they have to but detail why they do not wish to go to the CRAC.

Statistical issue
Dr. Stockbridge informed the sponsor that when looking at the mortality results cohort prior to the interim analysis used to resize the trial and the cohort subsequent to that, there was a notably large difference between them. Dr. Hung has begun trying to figure it out, looking at the baseline characteristics to understand why there is such a large difference. Furthermore, it is difficult for us to see if concomitant medication changes in subsequent analysis because the data set provided has over 2,000 distinct drug names with no drug class. Dr. Stockbridge asked that they obtain some insight as to why there is such a large difference.

In an earlier email, Dr. Hung provided the sponsor with a table, Table 2, which looked at the risk reduction. The sponsor will review the table and provide the Division with feedback.

PLANS:

1. NDA 20-727 will go to the CRAC on June 16, 2005. The sponsor should contact the Office of Advisors and Consultants for any questions about the CRAC, but are welcome to contact the Division. The sponsor is also welcome to submit a letter for the Office to reconsider our decision.
2. Ms. Carol Gloff will contact Ms. Paraoan about setting up the two meetings prior to submitting their briefing package and prior to the CRAC.
3. NitroMed, Inc. will provide the Division a response regarding the above issues on a) concomitant medication and b) temporal trends in risk reduction.

Norman Stockbridge, M.D., Ph.D.
Acting Director
Division of Cardio-Renal Drug Products

Draft: 4/15/05 Final: 4/27/05
RD:
Stockbridge: 4/27/05
Fromm: 4/27/05
Karkowsky: 4/26/05
Hung: 4/25/05

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/s/

Dianne Paraoan
4/28/05 03:05:25 PM
CSO

Norman Stockbridge
4/29/05 06:51:32 AM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

2-3-05

NDA 20-727

NitroMed, Inc.
Attention: Michael Sabolinski, M.D.
125 Spring Street
Lexington, MA 02421

Dear Dr. Sabolinski:

We acknowledge receipt on December 23, 2004, of your December 21, 2004 resubmission to your new drug application for BiDil® (isosorbide dinitrate/hydralazine HCl) Tablets.

We consider this a complete, class 2 response to our July 2, 1997 action letter. Therefore, the user fee goal date is June 23, 2005.

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. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application.

We have reviewed the submission and do not agree with a waiver of pediatric studies in patients less than 1 month to 16 years is justified for BiDil Tablets for the treatment of heart failure in black patients. However, the requirements for studies in pediatric patients are listed below:

1. Deferred pediatric studies under the Pediatric Research Equity Act (PREA) for the treatment of heart failure in pediatric patients ages 6 to 16 years of age.

2. Waived pediatric studies under PREA for the treatment of heart failure in pediatric patients ages <1 month to <6 years of age.

Accordingly, a waiver for pediatric studies for this application is denied under 21 CFR 314.55 at this time. We are deferring submission of your pediatric studies until December 23, 2006. Please submit your pediatric drug development plan by May 9, 2005.

If you have any questions, please call:

Ms. Dianne Paraoan
Regulatory Project Manager
(301) 594-5308

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Edward Fromm
2/3/05 10:05:34 AM

30 Day Meeting Minutes

DATE: January 18, 2005

NDA # 20-727
Trade Name: BiDil
Generic Name: hydralazine HCl and isosorbide dinitrate Tablets
Strengths: 37.5 mg hydralazine HCl /20 mg isosorbide dinitrate

Applicant: NitroMed, Inc.

Date of Submission:	December 21, 2004
Date of Receipt:	December 23, 2004
Date of 30 day Meeting:	January 18, 2005
User Fee Goal Date:	June 23, 2005

Indication requested: Treatment of heart failure in black patients.

BACKGROUND:

On July 2, 1997, Medco Research, Inc. received a non approvable letter for BiDil (hydralazine HCl and isosorbide diniatrate) with a propose indication of the treatment of congestive heart failure. The non approvable letter sited several medical, chemistry, and clinical pharmacology deficiencies. Since then, the sponsor, now NitroMed, Inc., has submitted a series of submissions resolving the listed chemistry and clinical pharmacology deficiencies.

As recommended by the Division in the non approvable letter, the sponsor conducted an additional trial which provides the results from the African American Heart Failure Trial (A-HeFT), which has been preformed in a black heart failure population, and per the sponsor, demonstrates clearly the positive results with BiDil.

NitroMed has now provided the Division with a complete response to their July 2, 1997 non approvable letter. The sponsor seeks an indication for the treatment of heart failure in black patients.

ATTENDEES:

Robert Temple, M.D.	Director, Office of Drug Evaluations I
Norman Stockbridge, M.D., Ph.D.	Acting Director, Division of Cardio-Renal Drug Products
Thomas Marciniak, M.D.	Acting Deputy Director
Abraham Karkowsky, M.D., Ph.D.	Team Leader, Medical
Salma Lemtouni, M.D., MPH	Medical Officer
Jim Hung, Ph.D.	Team Leader, Statistics
Kris Raman, Ph.D.	Chemist
Albert DeFelice, Ph.D.	Team Leader, Pharmacology
Charles Resnick, Ph.D.	Team Leader, Pharmacology
Peter Hinderling, M.D.	Clinical Pharmacology
Ed Fromm	Chief, Project Management Staff
Dianne Paraoan	Regulatory Health Project Manager

ASSIGNED REVIEWERS:

Discipline	Reviewer	Expected Completion Date
Medical:	Salma Lemtouni, M.D., MPH	April 15, 2005
Secondary Medical:	Norman Stockbridge, M.D., Ph.D.	
Statistical:	Jim Hung, Ph.D.	April 15, 2005
Pharmacology:	Al DeFelice, Ph.D.	April 15, 2005
Chemistry:	Kris Raman, Ph.D.	April 15, 2005
Environmental Assessment (if needed):		
Biopharmaceutical:	Peter Hinderling, M.D.	April 15, 2005
Microbiology, sterility:		
DSI:		
Regulatory Project Management:	Dianne Paraoan	

Per reviewers, are all parts in English or English translation? YES

CLINICAL
Dr. Lemtouni stated that the information provided seems to be complete.

The sponsor submitted a request for a Pediatric Waiver. The Division decided to deny the waiver and grant a deferral and request the sponsor to provide a preliminary plan around the time of their action date, June 23, 2005.

STATISTICS
Dr. Hung stated that the information provided is a complete response. The sponsor is to provide interim analysis data by the end of the week.

BIOPHARMACEUTICS
In the non-approvable letter, there were three clinical pharmacology issues identified. Dr Hinderling stated that the sponsor has addressed all issues, but he wanted clarification on the dissolution specifications. Dr. Hinderling will research prior submissions to include the IND to ensure that the dissolution issue has been resolved.

Note: After the meeting, Dr. Hinderling stated that he has no pending Clinical Pharmacology issues.

PHARMACOLOGY
Dr. DeFelice stated that there are no Pharmacology/Toxicology issues.

CHEMISTRY
Dr. Raman stated that the information provided is a complete response.

REGULATORY CONCLUSIONS/DEFICIENCIES:

The December 21, 2004 submission is a complete response to the July 2, 1997 non approvable letter.

ACTION ITEMS:
- Acknowledgement letter will include Pediatric Waiver.

Dianne C. Paraoan
Regulatory Health Project Manager, HFD-110

Draft: 2/3/05 Final:
RD

Stockbridge: 3/1/05
Fromm: 3/01/05
Karkowsky: 2/28/05
Marciniak: 2/23/05
Lemtouni: 2/22/05
DeFelice: 2/22/05
Resnick: 2/15/05
Hinderling: 2-14-05
Hung: 2-14-2005
Raman: 2/7/05

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/s/

Dianne Paraoan
3/1/05 01:14:12 PM

Minutes of a meeting between NitroMed and the FDA Division of Cardio-Renal Drug Products

Sponsor:	NitroMed Inc.
Drug:	BiDil (hydralazine HCL and isosorbide dinitrate) Tablets
IND:	41,816
Date of request:	July 13, 2004
Date request received:	July 13, 2004
Date of confirmation:	July 14, 2004
Date of meeting:	July 15, 2004
Time:	3:30-4:30 PM
Type/Classification:	C/Guidance Meeting
Classification:	Guidance/to discuss the BiDil DSMB recommendation and the extension of A-HeFT trial
Meeting Chairs:	Robert Temple, M.D. Norman Stockbridge, M.D., Ph.D.
Meeting recorders:	John David Denise M. Hinton

FDA Attendees:

Robert Temple, M.D.	Director, Office of Drug Evaluation I
Norman Stockbridge, M.D., Ph.D.	Acting Director, Division of Cardio-Renal Drug Products, HFD-110
Thomas Marciniak, M.D.	Medical Officer Team Leader, HFD-110
Salma Lemtouni, M.D., M.P.H.	Medical Officer, HFD-110
John David	Regulatory Health Project Manager, HFD-110
Denise Hinton	Regulatory Health Project Manager, HFD-110

NitroMed participants:

Michael Loberg, Ph.D.	Chief Executive Officer
Manuel Worcel, M.D.	Chief Medical Officer
Mike Sabolinski, Ph.D.	Senior VP, Clinical Development and Regulatory Affairs
Carol Gloff, Ph.D.	Vice President, Regulatory Affairs
[illegible]	FoxKiser
[illegible]	FoxKiser
[illegible]	FoxKiser
Ralph D'Agostino, Jr.	Ph.D., Consultant

Background:
NitroMed requested this meeting to provide an overview of the DSMB recommendation to stop the A-HeFT trial due to statistically significant mortality benefit over placebo in African American patients with heart failure and to discuss their proposal to extend the A-HeFT trial for BiDil (hydralazine HCL and isosorbide dinitrate) Tablets. NitroMed submitted an open label extension trial for A-HeFT and a BiDil NDA Amendment Plan for discussion.

Discussions:

Dr. Temple asked if death and hospitalizations were secondary endpoints and which endpoint represented a component of the composite endpoint for the heart failure scale. NitroMed stated that death and hospitalization were not secondary endpoints and explained that the components were quality of life (QOL), heart failure and death. NitroMed gave a detailed explanation of the scoring method of the composite endpoint and the weights given to each of its components. NitroMed asked if pharmacological toxicology is needed. The agency stated that no pharmacological toxicology studies are needed.

NitroMed stated that their plan is to stop the trial on Friday, as advised by the DSMB and requested feedback from the Agency on how to proceed. They plan to maintain the blind on an individual patient level while waiting to respond to the recommendations posed by the two committees (DSMB & A-HeFT Steering Committees). The Agency has no objections to NitroMed's proposal. In response to NitroMed's question of how they should manage the A-HeFT patient database, the Agency stated that the draft outline of the open label protocol, on its face, appeared adequate, however we will provide feedback after it is completely reviewed and if additional information is needed.

NitroMed discussed the BiDil NDA Amendment Plan and stated that they would clean up the datasets within 3 months. They are confident that they have sufficient data to launch commercial supplies and asked how they could expedite bringing there product to market. The Agency recommended that NitroMed submit the CMC information as early as possible and that the clinical data could be submitted in December [After the call ended the Agency reconsidered and recommended that the clinical data be submitted as soon as available.], as proposed.

Dr. Temple recommended that they provide information to address any issues or deficiencies raised in the past submission of NDA 20-727 and any further historical data that may aid in the review. NitroMed agreed to provide the requested information in the submission and stated that responses to the CMC and efficacy issues noted in the July 2, 1997 Not-Approvable letter were previously submitted. NitroMed was told to re-submit their application in follow-up to the Not-Approvable letter and to request a separate meeting with the Chemists to address CMC issues. The trademark name and labeling will need to be reviewed again as well.

The Agency offered to provide guidance to assist NitroMed with their NDA submission as needed and requested that the sponsor submit 1) SAS datasets, 2) annotated case report forms, 3) the original protocol 4) the base outline of the study report, and 5) all transactions with the DSMB.

Summary of Main Action Items (BiDil)

The Agency recommended that NitroMed do the following:

- Re-submit their application in follow-up to the not-approvable letter for NDA 20-727
- Schedule meetings with the Agency to discuss CMC issues
- Submit 1) SAS datasets, 2) annotated case report form, 3) protocols and 4) every transaction with the DSMB

Meeting recorders: _____
John David

_____
Denise Hinton

Meeting concurrence: _____
Robert Temple, M.D.

Draft: 16Jul04
Final: 3Aug04

RD:
Marciniak 7/27/04
Lemotouni 7/23/04
Stockbridge 7/29/04
Temple 8/2/04

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/s/

John David
8/3/04 02:47:19 PM

Denise Hinton
8/3/04 02:49:07 PM

Robert Temple
8/3/04 07:05:39 PM

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

Transmitted to FAX Number:	(781) 275-2282
Attention:	Dr. Carol Gloff
Company Name:	NitroMed
Phone:	(781) 685-9785
Subject:	**Biopharm Reviewer's Comments for BioWaiver Request for NDA 20-727 Ser#s 113 (June 13, 2003) and 114 (July 30, 2003) BiDil (hydralazine HCl/Isosorbide Dinitrate)**
Date:	August 5, 2003
Pages including this sheet:	**2**
From:	**Edward Fromm**
Phone:	**301-594-5332**
Fax:	**301-594-5494**

RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed NDA 20-727, Submission 113 dated June 13, 2003 and Submission 114, dated July 30, 2003 and has the following comments:

1. The non-bioproblem category for drugs approved before 1962 that the sponsor has referred to for justification of a biowaiver is no longer employed by the Agency. The sponsor is directed to refer back to the recent edition of the FDA Orange Book.

2. A bioequivalence study is required between the lower strength (37.5/20 mg) being used in the African-American Heart Failure Trial (A-HeFT) and the higher strength of 70/40 mg because HZN and ISDN exhibit nonlinear pharmacokinetics. Since previous data indicates

nonlinearity with higher doses of ISDN and HZN, a biowaiver can not be granted. Please refer to the FDA guidance entitled: Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations.

In the mentioned guidance, it is clearly stated that drugs that demonstrate nonlinear pharmacokinetics can not waive up for higher strengths. However, the sponsor may conduct a bioequivalence trial with a parallel design instead of the traditional crossover design due to the adverse events (mainly headache) previously observed in study CB01 that caused a large dropout rate (9 out of 12 subjects).

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/s/

Edward Fromm
8/5/03 02:59:37 PM
CSO

Minutes of a Telecon between NitroMed and the FDA

Date: June 25, 2002

Application: IND 41,816
NDA 20-727
BiDil (hydralazine HCl and isosorbide dinitrate) Tablets

Indication: Treatment of Congestive Heart Failure

Applicant: NitroMed

Subject: CMC Deficiencies in Not Approvable Letter

FDA participants

Kasturi Srinivasachar, Ph.D., HFD-810, Team Leader, Division of New Drug Chemistry I
J.V. Advani, Ph.D., HFD-810, Chemist
Edward Fromm, HFD-110, Regulatory Health Project Manager

NitroMed

Carol A. Gloff, Ph.D., Vice President, Regulatory Affairs
Dave Garvey, Ph.D., Senior Director of Chemistry
[ ] , Consultant

Background

NitroMed submitted on November 20, 2002, responses to the chemistry deficiencies listed in the July 2, 1997 Not-Approvable letter from the Agency. The sponsor requested a telecon with the Division chemists to get their feedback on the responses and whether those answers submitted were sufficient to constitute a "complete response" with regard to the chemistry deficiencies of the not-approvable letter.

Telecon

The Division and Nitromed discussed the 3 chemistry deficiencies from the July 2, 1997 Not-Approvable letter:

Deficiency #1-We still do not believe that you have adequately addressed the possibility of an interaction between the drug substances to form N-nitrosamines, products that have the potential to be carcinogenic.

Please test tablets from several of your oldest batches for the presence of nitrosamines to determine if these compounds are present, and if so, at what concentration.

Dr. Advani said the data sent in the November 20, 2002 submission was acceptable and answered Deficiency #1 of the not approvable letter.

Deficiency #2-Please provide the thermal stress studies data obtained by gradient HPLC. The data should indicate a mass balance of the amounts of the decomposed and related substances with the active ingredients of BiDil tablets.

Dr. Advani said that he had reviewed the data and it appears to be acceptable but said the sponsor should include this data in their validation package when submitting their NDA. After review by the chemist, the data will be forwarded to the FDA's District Laboratories.

Dr. Srinivasachar noted that the thermal stress studies and stability studies indicate the presence of 2 degradents identified as pthalzaine and phthalazinone. He said that firm should follow the ICH guidelines to qualify these impurities by animal safety data or clinical trial results.

Deficiency #3-Based on the analytical results, the NDA method appears not to be suitable for regulatory control of the product. One extra large peak was found in method [ ] that was not identified and the [ ] for the compound are significantly different from the one shown in the method. We also note that the product did not meet your specifications for impurities of NMT [ ] Impurity amounts in the [ ] lots tested were [ ] Please clarify.

Dr. Advani said the current validation procedure appears satisfactory, but noted that it should be updated and included with the application when it is resubmitted. A copy of the methods validation package will also be sent to the FDA District Laboratories for review.

Minutes Preparation: _____
Edward Fromm

Concurrence: _____
Kasturi Srinivasachar, Ph.D.

dr/ef-6-27-02/6-28-02

Rd: JAdvani-6-27-02

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/s/

Edward Fromm
6/28/02 02:02:35 PM
CSO
Dr. Srinivasachar signed the minutes on June 28, 2002.

Edward Fromm
6/28/02 02:06:21 PM
CSO
Dr. Srinivasachar signed the minutes on June 28, 2002.

Minutes of a Telecon between NitroMed and the FDA

Date: April 6, 2001

Sponsor: NitroMed, Inc.

Subject: BiDil (hydralazine HCl and isosorbide dinitrate)
NDA 20-727

Type of Meeting: Discussion of clinical protocol for the treatment of African-American patients with CHF

FDA Participants:

Douglas Throckmorton, M.D., HFD-110, Deputy Division Director
Norman Stockbridge, M.D., Ph.D., Medical Team Leader
James Hung, Ph.D., HFD-110, Statistician/Team Leader
Edward Fromm, HFD-110, Project Manager

NitroMed

Michael Loberg, Ph.D., Chief Executive Officer
Manuel Worcel, M.D., President
[ ] Consultant,
Ralph D'Agostino, Ph.D, Consultant
Carol Gloff, Ph.D., Consultant
[ ] Consultant

Background

NitroMed submitted on January 29, 2001, a protocol outline (with revisions suggested by the Agency) for the use of BiDil in the treatment of CHF in African-American patients. The Agency, in a letter to the firm on March 2, 2001, confirmed that the protocol outline was acceptable but asked the company to submit a detailed protocol to the Division for review and comment.

NitroMed sent in a complete protocol to the Division on March 15, 2001 and asked for a telecon with the Division to discuss any comments or suggestions the Division had regarding it.

Telecon

Dr. Throckmorton opened the telecon by noting that the primary endpoint had changed to one that would adequately address clinical efficacy if the trial is successful. He added that a statistical analysis would have to verify the robustness of the data.

Nitromed asked if the protocol submitted is consistent with the protocol outline sent in earlier to the Division. He said the protocol submitted is consistent with the outline; he said, however, that the Division was concerned that the pre-specified composite endpoint of mortality and morbidity parameters could be driven by the morbidity part of the endpoint.
Dr. Throckmorton said that a $p<0.05$ (as specified in the protocol) might not be sufficient to support efficacy of the drug under certain conditions. For example, if the p-value for the study was reported at 0.048 but the data leaned in the wrong direction for mortality, the study (when compared to VeHFT I) might be judged by the Division as not supportive of efficacy. He also said that this type (placebo-controlled) trial would be difficult to undertake again if

unsuccessful. To reduce this risk, the firm should try to increase sample size so as to achieve a more significant p-value. The firm asked what p-value should they aim for. Dr. Throckmorton said he could not give an absolute answer. He also mentioned that increasing sample size would tighten the boundaries for the interim analysis and add robustness to the study.

Nitromed asked if the sample size could be increased after the interim analysis was completed. Dr. Throckmorton said this was acceptable, subject to the rules of the interim analysis.

The firm asked if they changed the p-value of the protocol, would they need to send in a new protocol or could they just send in a letter notifying the Division of the change. Dr. Throckmorton said it would be acceptable to just send in a letter noting the change.

Conclusion

Dr. Throckmorton said the protocol was acceptable to the Division but suggested that the firm should increase the power of the study to better detect a highly significant effect of the drug. He said that an increase in sample size could come after the interim analysis.

Minutes Preparation: _____
Edward Fromm

Concurrence: _____
Douglas Throckmorton, M.D.

dr/ef-04-06-01/04-11-01

Rd: JHung-4/6/01
NStockbridge-4/10/01

/s/

Edward Fromm
4/11/01 08:36:54 AM
Dr. Throckmorton signed the minutes on April 11, 2001

Minutes of a Telecon between NitroMed and the FDA

Date: January 24, 2001

Sponsor: NitroMed, Inc.

Subject: BiDil (hydralazine HCl and isosorbide dinitrate)
NDA 20-727

Type of Meeting: Discussion of revised outline of clinical protocol for the treatment of African-American patients with CHF

FDA Participants:

Robert Temple, M.D., HFD-101, Director, Office of Drug Evaluation and Research
Raymond Lipicky, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products
Douglas Throckmorton, M.D., HFD-110, Deputy Division Director
Norman Stockbridge, M.D., Ph.D., Medical Team Leader
James Hung, Ph.D., HFD-110, Statistician/Team Leader
Lu Cui, Ph.D., HFD-710, Biostatistician
Emmanuel Fadiran, Ph.D., HFD-860, Clinical Pharmacologist and Biopharmaceuticist
J.V. Advani, Ph.D., HFD-810, Chemist
Kasturi Srinivasachar, Ph.D., HFD-810, Team Leader, Division of New Drug Chemistry I
Natalia Morgenstern, HFD-110, Chief, Project Management Staff
Edward Fromm, HFD-110, Project Manager

NitroMed

Michael Loberg, Ph.D., Chief Executive Officer
Manuel Worcel, M.D., President
Thomas Conrad, Ph.D.. MPH, RNC, Director, Regulatory Affairs
[ ] Consultant, [ ]
[ ] Consultant, [ ]

Background

NitroMed submitted on January 19, 2001, a draft protocol outline (with revisions suggested by the Agency) for the use of BiDil in the treatment of CHF in African-American patients. The sponsor requested a telecon with the Agency to get their feedback on the draft outline.

Telecon

Dr. Temple opened the telecon by noting that the Agency had two primary objections to the draft study outline that was recently submitted:

1) LVEF (Left Ventricular Ejection Fraction) was part of a composite primary endpoint and it would probably dominate the other three endpoints (death, hospitalizations, and QOL (Quality of Life) data). NitroMed replied that they believe that ejection fraction improvement should be included in the primary endpoint as they believe that it correlates with positive morbidity and mortality outcomes. Dr. Temple said there is no clear evidence that ejection fraction improvement correlates with favorable morbidity and mortality outcomes and that the inclusion of ejection fraction as a primary endpoint in the proposed study was unacceptable to the Agency. He

noted that the firm was already measuring symptom improvement (QOL) and outcomes (death, hospitalizations) associated with ejection fraction and therefore the inclusion of it as a primary endpoint would seem redundant, at least if it corresponded to a clinical benefit. The firm said they would discuss the ejection fraction issue internally and would inform the Agency of how they wish to proceed as soon as possible.

2) The Agency needs more information on how the sponsor proposes to adjust the sample size to achieve appropriate power with respect to the primary endpoints. Dr. Temple suggested that the firm contact the Division statistician, Dr. James Hung, to obtain assistance with this issue.

Nitromed asked the Agency if the rest of the draft outline provisions were acceptable. Dr. Temple responded it appears to be acceptable but noted that they had not yet submitted a detailed protocol to the Division. He said, however, that when they send in a revised study outline that is acceptable to the Agency, he would be open to issuing a letter to the company stating that a trial with convincing results could result in approval of BiDil in the treatment of CHF for African-American patients.

Minutes Preparation:

Edward Fromm

Concurrence:

Robert Temple, M.D.

dr/ef-01/25/01-02/07/01-02/15/01

Rd: J.V. Advani-1/26/01
KSrinivasachar-1/26/01
EFadiran-1/26/01
LCui-1/26/01
JHung-01/27/01
NStockbridge-1/30/01
DThrockmorton-1/30/01
NMorgenstern-2/06/01

/s/

Edward Fromm
2/20/01 10:25:58 AM
Dr. Robert Temple signed the minutes on February 20, 2001

Minutes of a Telecon between NitroMed and the FDA

Date: January 23, 2001

Sponsor: NitroMed, Inc.

Subject: BiDil (hydralazine HCl and isosorbide dinitrate)

Type of Meeting: CMC deficiencies from not-approvable letter

FDA Participants:

J.V. Advani, Ph.D., HFD-810, Chemist
Kasturi Srinivasachar, Ph.D., HFD-810, Team Leader, Division of New Drug Chemistry I
Edward Fromm, HFD-110, Project Manager

NitroMed

Manuel Worcel, M.D., President
Thomas Conrad, Ph.D., MPH, RNC, Director, Regulatory Affairs
Dave Garvey, Ph.D., Senior Director of Chemistry
[redacted], Consultant

Background

NitroMed submitted on January 8, 2001, responses to the chemistry deficiencies listed in the July 2, 1997 Not-Approvable letter from the Agency. The sponsor requested a telecon with the Division chemists to get their feedback on the responses and whether those answers submitted were sufficient to constitute a "complete response" with regard to the chemistry deficiencies of the not-approvable letter.

Telecon

The Division and Nitromed discussed the 3 chemistry deficiencies from the July 2, 1997 Not-Approvable letter:

Deficiency #1-We still do not believe that you have adequately addressed the possibility of an interaction between the drug substances to form N-nitrosamines, products that have the potential to be carcinogenic.

Please test tablets from several of your oldest batches for the presence of nitrosamines to determine if these compounds are present, and if so, at what concentration.

NitroMed said, for (chemical) mechanistic reasons, that nitrosamines should not be formed when isosorbide dinitrate and hydralazine are mixed together to form a single tablet. Dr. Advani said it would be helpful, nevertheless, to determine if any levels of nitrosamines are present. The firm said this would be difficult as there are no standards for measuring nitrosamines.

Dr. Srinivasachar asked the firm if there was any evidence of pthalazine as a decomposition byproduct of BiDil. The firm responded by noting that there was some evidence from stability studies of pthalazine and 1-(2H)-phthalazinone degradents. Dr. Srinivasachar said the firm would need to qualify impurities and degradents by animal safety data or clinical trial results. The firm

said it would check the pharm/tox data from the original NDA submission to see if the pthalazine and phthalazinone degradents were studied.

Deficiency #2-Please provide the thermal stress studies data obtained by gradient HPLC. The data should indicate a mass balance of the amounts of the decomposed and related substances with the active ingredients of BiDil tablets.

Dr. Advani noted that the sponsor said that the thermal stress studies data could not be located; he said this and the mass balance data were important to the Division and would have to be submitted for the product. The firm said the thermal stress studies and mass balance data were part of the validation procedure and would be submitted to the Division when that process was complete. Dr. Srinivasachar said this was acceptable.

Deficiency #3-Based on the analytical results, the NDA method appears not to be suitable for regulatory control of the product. One extra large peak was found in method [ ] that was not identified and the [ ] for the compound are significantly different from the one shown in the method. We also note that the product did not meet your specifications for impurities of NMT [ ] Impurity amounts in the four lots tested were : [ ] [ ] Please clarify.

Dr. Advani said that the January 8, 2001 amendment from the sponsor did not adequately address the inadequacy of the HPLC validation method used by Medco; he said the FDA labs were not able to reproduce the validation method used by the sponsor in the original NDA application. Dr. Srinivasachar noted that [ ] impurity levels were found by Medco during the HPLC validation and said these would also need to be addressed by the sponsor. The sponsor said their plan was to use Medco's method as a starting point, but noted that they would be generating validation data on the new batches of drug and would be looking closely at impurity levels. They added that they plan to submit the new validation data to the Division by mid-March, 2001 and would have impurity readouts (from 1 month accelerated stability studies) by the end of March or April. Dr. Advani said that after receipt of the validation data it would take approximately 3 months for the Agency labs to complete their evaluation of the data.

Expiration dating

Dr. Srinivasachar asked the firm how they plan to justify expiration dating for BiDil. The firm replied that they would have [ ] accelerated stability data by early summer but would not have 12-month room temperature data until March 2002. Dr. Srinivasachar reminded the firm that the new ICH guidelines call for 6 months accelerated data prior to approval of the product.

Manufacturer of Product

Dr. Srinivasachar asked the firm if there were any changes in the drug substance or manufacturer since the original NDA submission. The firm said they would be using the same drug substance but would have a new manufacturer, Schwarz Pharma. Dr. Srinivasachar noted that the new manufacturer would be subject to an Agency inspection once the NDA was resubmitted to the Division.

Conclusion

Dr. Srinivasachar said that the chemistry deficiencies from the not-approvable letter for BiDil have not been adequately addressed at this point and therefore the sponsor's amendment of January 8, 2001 could not be considered a "complete response" to the chemistry deficiencies listed in the not-

approvable letter. He also noted that that the firm has a new manufacturer of the product and that this facility would be subject to inspection once the NDA has been resubmitted to the Division.

Minutes Preparation: _____
Edward Fromm

Concurrence: _____
Kasturi Srinivasachar, Ph.D.

dr/ef-01/23/01-01/25/01

Rd: J.V. Advani-01/24/01

/s/

Edward Fromm
1/25/01 04:31:34 PM
Dr. Srinivasachar signed minutes on Jan. 25, 2001

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

Transmitted to FAX Number:	(781) 275-2282
Attention:	Dr. Michael Loberg
Company Name:	NitroMed Inc.
Phone:	(781) 685-9795
Subject:	**Biopharm comments in response to January 8, 2001 submission to the FDA NDA 20-727**
Date:	04/16/01
Pages including this sheet:	**2**
From:	**Edward Fromm**
Phone:	**301-594-5313**
Fax:	**301-594-5494**

Dear Dr. Loberg:

Please note the Biopharm comments regarding your submission of January 8, 2001 for NDA 20-727, BiDil, (hydralazine/isosorbide dinitrate) Tablet, 37.5/20mg. The 3 comments referred to in the attachment are those that were listed in the July, 1997 not-approvable letter.

If you have questions or comments, please call me at the above number.

Thanks,

Ed

FDA COMMENT 3: *Your proposal for inclusion of information regarding food-effect on hydralyzine and isosorbide dinitrate based on published literature cannot be accepted. A food-effect study, using to be marketed formulation of BiDil will be required to support any statement relating to the effect of food on administration of BiDil.*

NITROMED RESPONSE: *Product labeling has been revised accordingly (see below).*

Drug/Food Interactions
Studies of ISDN and hydralazine separately have not demonstrated evidence of food interactions. Because there are no data regarding the food effect on this particular formulation, it is recommend patients take this combination at least 30 minutes prior to meals.

REVIEWER'S COMMENT:
The **Drug/Food Interactions section of the BiDil labeling should state :**
"No information is currently available regarding the effect of food on BiDil tablets".

RECOMMENDATION:
The sponsor's responses to OCBP comments 1 and 2 are acceptable but the sponsor's response to OCPB comment 3 is not acceptable.

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

/s/

Edward Fromm
4/17/01 08:03:17 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-727

3-1-01

NitroMed, Inc.
Attention: Thomas M. Conrad, Ph.D., MPH, RNC
12 Oak Park Drive
Bedford, Massachusetts 01730

Dear Dr. Conrad:

Please refer to your new drug application (NDA) dated July 3, 1996 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for BiDil (hydralazine HCl and isosorbide dinitrate) Tablets and our meetings of July 21, 1999, April 5, 2000, and December 12, 2000.

We acknowledge receipt of your amendments dated July 28, 2000 and January 12, 19, and 29, 2001.

Post-hoc analyses of the results of VHeFT I and II suggest that BiDil might be associated with a survival benefit in blacks with heart failure. Given the subset finding and the overall trend toward a survival effect in VHeFT I, we believe a single, clearly positive study in a black CHF population would be a basis for approval of BiDil for the treatment of heart failure in blacks.

We have reviewed the outline of your proposed confirmatory provided in your submission of January 29, 2001 and have determined that if the results of the study are convincing this would provide sufficient clinical evidence to support approval of BiDil. A detailed protocol for the proposed study, including a statistical plan, should be sent to the Agency for our review and comments.

Please note that deficiencies listed in the July 2, 1997 not-approvable letter will also need to be corrected before approval of BiDil can be entertained.

If you have any questions, please contact:

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

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

/s/

Robert Temple
3/1/01 07:02:11 PM

Minutes of a Meeting between NitroMed and the FDA

Date: December 12, 2000

Sponsor: NitroMed, Inc.

Subject: BiDil (hydralazine HCl and isosorbide dinitrate)

Type of Meeting: Discussion of new protocol

FDA Participants:

Robert Temple, M.D., HFD-101, Director, Office of Drug Evaluation and Research
Douglas Throckmorton, M.D., HFD-110, Deputy Division Director
Abraham Karkowsky, M.D., Ph.D., HFD-110, Medical Team Leader
James Hung, Ph.D., HFD-110, Statistician/Team Leader
Lu Cui, Ph.D., HFD-710, Biostatistician
Natalia Morgenstern, HFD-110, Chief, Project Management Staff
Edward Fromm, HFD-110, Project Manager
Quynh Nguyen, Pharm.D., HFD-110, Project Manager

NitroMed

Michael Loberg, Ph.D., Chief Executive Officer
Thomas Conrad, Ph.D., MPH, RNC, Director, Regulatory Affairs
Jay Cohn, M.D., Professor, University of Minnesota, Cardiovascular Division
[redacted]

Background

NDA 20-727 provides for the use of BiDil for the treatment of congestive heart failure. On July 2, 1997, a not-approvable letter was issued to the applicant, Dr. Jay Cohn. Dr. Cohn transferred the BiDil application to NitroMed in September, 1999. NitroMed requested a meeting with the Agency to discuss a new protocol, that, combined with data from the V-HeFT 1 trial, would yield data to support an indication for BiDil in the treatment of heart failure in black patients.

Meeting

The firm opened the meeting by stating that they were proposing a study that would confirm the favorable, retrospective, subset analysis in black patients for mortality found in the V-HeFT 1 trial. They also believed that there was a positive effect on exercise tolerance (maximal oxygen consumption) in the V-HeFT 2 trial. Dr. Temple said there was a trend in V-HeFT 1 that showed decreased mortality in black patients, but because the trend was discovered retrospectively, the Agency found difficulty in accepting this reanalysis as a "single trial" by itself. Furthermore, the V-HeFT 2 trial, the very trial one would conduct to compare BiDil with an ACE inhibitor in blacks (expecting an advantage), showed no mortality advantage for BiDil. Dr. Temple said that we were not convinced there was a positive effect on exercise tolerance in V-HeFT 2 but that we would review the exercise tolerance data internally as well as the V-HeFT 1 data.

Proposed Trial

Nitromed said it was proposing a confirmatory, placebo-controlled trial to show the safety and efficacy of BiDil in black patients with symptomatic Heart Failure. The proposed primary endpoints of the study are QOL (Quality of Life) assessments and LVEF (Left Ventricular Ejection Fraction). The firm also noted that they were prepared to change the NYHA entry criteria from NYHA ≥II patients to NYHA III and IV patients, even though it would probably make recruitment for the study more difficult.

Dr. Throckmorton asked what is the entry criterion for ejection fraction. The firm said they plan on accepting patients with ejection fractions below 35%. Dr. Temple said he thought ejection fraction was not a good primary endpoint. The firm disagreed, saying that ejection fraction improvement could serve as an indicator of mortality benefit. They noted that they included LVIDD (Left Ventricular Internal Diameter at End-Diastole) as a secondary endpoint because they believe that BiDil will alter the structural integrity of the heart to produce favorable outcomes in heart failure patients. Dr. Temple said he believed that a correlation of ejection fraction with favorable outcomes was not clear; he said, however, that if the firm measured ejection fraction of patients at a timepoint 2 weeks after discontinuation of therapy and showed a persistence of effect, the Agency would give serious consideration to these data. He added that if the company pursues this option it should blind the reader of the echocardiograms.

Dr. Temple asked the company what Quality of Life assessment it was using. The firm said it would be using the Minnesota Living with Heart Failure assessment. Dr. Temple said it would be helpful to include global assessments, such as dyspnea and fatigue ratings. He said that Quality of Life (with a few modifications) was an acceptable primary endpoint but said that major morbidity and mortality (deaths, hospitalizations) should also be included as a primary endpoint. Dr. Temple noted that he believes that there will be enough of these events so that ER visits and unscheduled office visits will not have to be included in the primary endpoint. He preferred a time-to-a-first event analysis along with comparison of total events. The firm mentioned that they would have about 100 events per arm and asked the Agency if that would be sufficient. Dr. Temple said the answer to that question would depend on the percent reduction in morbidity/mortality that the firm wishes to achieve; he said the p value for the trial should be ≤ 0.05. The company said that they believed that they could show positive trends with 300 patients per arm but not with a $p \leq 0.05$ certainty. Dr. Temple said that a positive effect on ejection fraction (as a secondary endpoint) could lend more credibility to the drug's effect in heart failure. He added that the primary endpoints of Quality of Life and a combined morbidity/mortality endpoint, with ejection fraction as a secondary endpoint, would probably require little additional spending of alpha and would include a primary endpoint (morbidity/mortality) that is included in most CHF trials.

Dr. Temple asked the firm if they would encourage concomitant medications (e.g., ACE inhibitors, diuretics, beta-blockers) during the proposed trial. The firm said that they would ensure all patients would be on optimal therapy; they noted that patients would be stabilized on their medications for at least 2 weeks prior to the beginning of the study. Dr. Temple also noted that the 6-month followup of patients after the end of the trial was acceptable.

Dr. Temple asked the company if they would stratify for beta-blocker use during the trial. The firm said they would stratify for beta-blocker use during the trial.

Subpart H-Accelerated Approval

Nitromed asked if they could do their proposed study under conditions for subpart H. Dr. Temple said, with the possible exception of ejection fraction, the endpoints the firm has outlined in their protocol are not "reasonable surrogates" as defined under subpart H, but are in fact clinical endpoints, so that there is no need to use the accelerated approval route. He said the firm could do an ejection fraction trial (i.e., one with a surrogate endpoint) but it would need to be replicated by another successful trial prior to approval of the drug. Dr. Temple noted that such a trial would have to answer two questions (in the CHF population):

1) How long would the positive effect of BiDil on ejection fraction last.
2) What would be the magnitude of BiDil's effect be on ejection fraction.

Approvable letter

Nitromed submitted an amendment to the NDA in July, 2001 that they said responded to the July 2, 1997 not-approvable letter sent by the Agency. The firm asked if the Agency would issue an approvable letter with the understanding that the firm would complete a successful trial prior to approval of the drug. Dr. Temple said the July amendment did not provide a complete response to all the deficiencies (e.g., chemistry) that were listed in the not-approvable letter and therefore no action letter was necessary or planned. He also said that the Agency had not concluded that the subset analysis in V-HeFT 1 was a "single successful trial", although it certainly could support other results when they are available. Dr. Temple did say, however, that he was open to issuing a letter for the firm stating that a successful trial (with modifications suggested by the Agency) may result in approval of the drug. He encouraged the firm to revise their protocol accordingly and send it in to the Division for review.

Conclusion

Dr. Temple suggested that the firm submit a revised protocol into the Division for review. He also said he was willing to issue a letter stating that one more successful trial (with revisions suggested by the Agency) could result in approval of BiDil. The exercise tolerance data from V-HeFT 2 will be reviewed internally as well as the subset reanalysis of V-HeFT 1.

Minutes Preparation: _____
Edward Fromm

Concurrence: _____
Robert Temple, M.D.

dr/12-22-00/1-04-01/1-09-01

Rd: QNguyen-12-22-00
LCui-12-22-00
JHung-12-22-00
DThrockmorton-1-04-01
NMorgenstern-1-04-01

/s/

Edward Fromm
1/11/01 04:57:46 PM
Minutes signed by Dr. Robert Temple on January 11, 2001

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

G. Buehler

NDA 20-727

JUL 2 1997

Medco Research, Inc.
Attention: Janice L. Parry, Pharm.D.
P.O. Box 13886
Research Triangle Park, NC 27709

Dear Dr. Parry:

Please refer to your July 3, 1996 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for BiDil (hydralazine HCl and isosorbide dinitrate) 37.5/10, 37.5/20, 75/20, and 75/40 mg Tablets.

We acknowledge receipt of your amendments and correspondence dated August 2, 9, 12 and 13, September 12 and 26, October 24, November 20, 21 and 26, December 11, 12, 13 and 18, 1996; January 2 (two), 9, 13, 23 (two), 27 (two) and 31, February 3 (two), 12 and 24 (two) and April 14, 1997.

We have completed our review and find the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

MEDICAL

The Cardiovascular and Renal Drugs Advisory Committee did not recommend approval of the combination of isosorbide dinitrate and hydralazine for the treatment of congestive heart failure. The Division of Cardio-Renal Drug Products and I concur with that recommendation.

The only support for approval is the mortality results of VHeFT I. There were fewer deaths in the combination treated population than there were in the placebo treated or prazosin treated populations. The p values for this difference (adjusted for multiple comparisons, multiple testing, interim analysis, etc.) vary from 0.019 to 0.11 (2-sided) depending on the analysis method, the imputation method utilized for missing covariants and overall vs. 2-year survival. Although the combination did not detect a symptomatic benefit (e.g., exercise tolerance, hospitalizations for congestive heart failure, hospitalizations for any reason, and either the patient or physician quality of life responses), a survival advantage would be a basis for approval. The results of VHeFT 1, however, are not convincing enough to support approval alone, particularly in light of the results of VHeFT II.

The other study conducted that could possibly offer confirmation of the VHeFT I mortality finding is VHeFT II. Unfortunately, VHeFT II was not placebo-controlled and the combination treatment was statistically significantly inferior to enalapril with respect

to 2-year mortality. Using a cross-study comparison of BiDil in VHeFT-II with the placebo in VHeFT-I, you have suggested that even though enalapril was superior to BiDil, BiDil in VHeFT-II could still be superior to no treatment. To conclude that BiDil is effective, one must believe that enalapril was more than 30% better on 2-year survival than the combination (VHeFT II) and that the combination in turn was more than 30% better than a placebo (had there been one) (i.e., the VHeFT I effect). That would require an overall effect (vs placebo) of enalapril of more than 50%, a far greater effect of enalapril than has been seen in symptomatic patients of any NYHA class. Indeed, the difference between enalapril and the combination in VHeFT II is greater (32% reduction at 2 years) than the difference between enalapril and placebo in the SOLVD treatment study (23% at 2 years).

CHEMISTRY

1. We still do not believe that you have adequately addressed the possibility of an interaction between the drug substances to form N-nitrosoamines, products that have the potential to be carcinogenic.

   Please test tablets from several of your oldest batches for the presence of nitrosoamines to determine if these compounds are present, and if so, at what concentration.

2. Please provide the thermal stress studies data obtained by gradient HPLC. The data should indicate a mass balance of the amounts of the decomposed and related substances with the active ingredients of BiDil tablets.

3. Based on the analytical results, the NDA method appears not to be suitable for regulatory control of the product. One extra large peak was found in method [ ] that was not identified and the [ ] for the compound are significantly different from the one shown in the method. We also note that the product did not meet your specifications for impurities of NMT [ ] Impurity amounts in the four lots tested were [ ] [ ] Please clarify.

In addition, we have the following comments and requests for information that should be addressed:

PHARMACOKINETICS

1. In view of the fact that the 37.5/10 mg tablet showed a slower dissolution performance compared to the 37.5/20, 75/20 and 75/40 in all 4 media tested, an in-vivo bioavailability waiver cannot be granted for the two middle strengths (37.5/20, 75/20). However, the multiple-dose study that you are currently conducting using all strengths in CHF patients could provide the necessary data.

2. When asked to provide the pharmacokinetic parameters for study CB02 in electronic form on diskette the only data submitted was for the normalized parameters to a weight of 65 kg. Upon review, it was discovered that the data on diskette did not match the data found in the NDA, and the discrepancy remains unexplained. In future submissions, please validate all data sets before they are submitted.

3. Your proposal for inclusion of information regarding food-effect on hydralazine and isosorbide dinitrate based on published literature cannot be accepted. A food-effect study, using the to-be-marketed formulation of BiDil, will be required to support any statement relating to the effect of food on administration of BiDil.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Should you have any questions, please contact:

Mr. Gary Buehler
Regulatory Health Project Manager
Telephone: (301) 594-5332

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDA
HFD-2/MLumpkin
~~HFD-110~~
HFD-110/Project Manager
HFD-92
HFD-101
DISTRICT OFFICE
HFD-810/New Drug Chemistry Division Director
HFD-110/GBuehler;4/18/97
sb/3/5/97;3/27/97;4/4/97;4/16/97;4/18/97;7/2/97
R/D RLipicky;4/18/97
ADeFelice/4/10/97;4/18/97
JAdvani/4/6/97
JShort for RWolters/4/4/97
PMarroum/4/4/97;6/18/97
CGanley/4/9/97;4/18/97;7/1/97
SChen/4/4/97;7/1/97;7/2/97
JHung/4/4/97;7/1/97
EBelair/4/10/97
NMorgenstern/4/15/97;4/17/97;4/18/97;7/1/97
RWolters/4/18/97;7/1/97

NOT APPROVABLE

7-1-97

APPLICATION SUMMARY UPDATE

NDA 20-727 BiDil (hydralazine HCl and isosorbide dinitrate) Tablets

Date: July 1, 1997

BACKGROUND

The review package for BiDil was returned to the Division on June 23, 1997 for revisions and corrections. The following issues were identified:

Chemistry

1. EER Not completed.
2. Chemistry review #3 did not have a draft letter.
3. Chemistry question #3 in the decision letter was misleading.

Pharmacology

1. Pharmacology memo of 2/24/97 was not signed.
2. Pharmacology review did not have supervisory sign-off, and there were issues noted in the review that were not addressed.

Medical

1. Dr. Temple revised the text of the decision letter.

ACTION

Chemistry

1. The EER was completed and is in the review package under "EER."
2. All deficiencies from Chemistry review #3 were addressed even though a draft letter was not prepared. The deficiency was noted for future reference.
3. Chemistry question #3 was revised.

Pharmacology

1. The unsigned pharmacology reviews and memos were signed.
2. Dr. DeFelice addressed the issues noted in the pharmacology review.

Medical

1. A meeting was held with Dr. Temple and the medical review team on 7/1/97 to address the revisions made in the decision letter. Consensus was reached at that meeting on the final text of the letter.

Gary Buehler
Project Manager

MEETING MINUTES

JUL 1 1997

Date: April 22, 1997 3:00 PM CR "F", WOC II

Subj: NDA 20-727 BiDil (isosorbide dinitrate/hydralazine HCl) Tablets

Meeting Chair: Robert Temple, M.D.
Recorder: Gary Buehler
Sponsor Lead: Jay Cohn, M.D.

Medco Attendees:

Jay Cohn, M.D.	Consultant to Medco
Joe Quinn	Statistician
Janice Parry, Pharm D	Regulatory Affairs
Cesare Orlandi, M.D.	Medical Director
Keith Schneider	Director, Regulatory Affairs

FDA Attendees:

Robert Temple, M.D.	Director, ODE I, HFD-101
Raymond Lipicky, M.D.	Dir., Div. of Cardio-Renal Drug Prod., HFD-110
Charles Ganley, M.D.	Medical Team Leader, HFD-110
Shaw Chen, M.D., Ph.D.	Medical Team Leader, HFD-110
James Hung, Ph. D.	Statistical Reviewer, Div. of Biometrics, HFD-710
Patrick Marroum, Ph.D.	Team Leader, Div. of Pharm. Science I, HFD-860
Isaac Hammond, M.D., Ph.D.	New Staff
Khin U, M.D.	New Staff
Femi Williams, M.D.	New Staff
Douglas Throckmorton, M.D.	New Staff
Gary Buehler	Project Manager, HFD-110

BACKGROUND

NDA 20-727 was submitted on July 3, 1996 for BiDil (isosorbide dinitrate/hydralazine HCl) Tablets. The application initially proposed the use of BiDil for a mortality claim in CHF patients who could not take ACE inhibitors. This was later revised to a claim for symptomatic relief for all CHF patients. Clinical support for the application was provided by the V-HeFT I and II trials. The viability of these trials serving as the basis for an NDA was discussed in meetings with the Division of Cardio-Renal Drug Products on February 12, 1991 (with Dr. Cohn and Wyeth-Ayerst) and November 20, 1992 (with Dr. Cohn and Medco).

On February 27, 1997 the BiDil application went before the Cardiac and Renal Drugs Advisory Committee. The Committee voted 8-3 to not approve the application because they did not believe that the data submitted met the regulatory standard for approval.

AGENDA

Medco asked to meet to have a frank discussion of their options for the BiDil NDA. They wanted to discuss the Advisory Committee decision and specifically the fact that the Committee chose to reject the advice given to the sponsor by the Division regarding the analysis for the V-HeFT I

trial. They also believed that the questions for the BiDil application set a different tenor and tone for the Committee discussion compared to the Coreg discussion held later the same day. They thought that this difference had an enormous impact on the Committee discussion and eventual recommendation.

DISCUSSION/DECISIONS

Advisory Committee/Previous commitments

Dr. Orlandi opened the meeting by stating that his firm was confused by what happened to the BiDil application at the Advisory Committee meeting; they still believe that the application is approvable. They believed that they came before the Committee through a series of steps involving numerous meetings with the Agency. While they understood that the analysis used for V-HeFT I was retrospective, they believed that it was considered acceptable by the Agency. He stated that this issue relates to all future dealings with the Agency in that they must be able to rely on advice given to them.

Response

Dr. Temple said that, judging from what was written in the minutes, he did not believe that we ever guaranteed an approvable application. We thought that the V-HeFT I trial, using the modified analysis, would help to form a reasonable package. When combined with the V-HeFT II trial, however, the marginal result was not replicated. As to what the decision would have been if V-HeFT II were not done, Dr. Temple said that the question was difficult to answer, but failure to confirm a positive result can be very damaging.

Old, Small Study

Dr. Cohn said that he recognized that the V-HeFT I trial did not have the power that one would want in this day for a mortality trial. He said that they should not be penalized for doing a landmark study. Because of the result, it is not possible to re-test the product for its mortality effect.

Response

Dr. Temple said that they were not being punished for the study being small. We recognized that the V-HeFT I trial was borderline. Again, the major problem was that V-HeFT II undermined the borderline mortality result by showing a substantial advantage of enalapril over BiDil. There did not seem to be "room" for a BiDil effect when we know the effect of enalapril is only 20% or so.

Recommendation of Foreign Experts

Dr. Cohn said that the combination of hydralazine HCl and isosorbide is recommended by many foreign organizations as therapy for patients with CHF who cannot take ACE inhibitors. He said it was the Agency's duty to label drugs appropriately for use so that practitioners in this country can use them safely.

Response

Dr. Temple said that he did not believe that the decisions of foreign organizations were compelling, nor did he believe that it was the Agency's responsibility to label drugs that do not meet the standard for approval, although we certainly would like more off-label uses that can be supported to be in labeling.

Use of Unproven Therapies/Not Precedent Setting

Dr. Cohn said that he believed that the mortality effect of ACE inhibitors in recent studies is under estimated because of improvements in ancillary care and that as used in V-HeFT II, it

would be larger. The mortality effect of BiDil, therefore, could lie somewhere between placebo and ACE inhibitors as shown in V-HeFT II. The product was clearly effective in V-HeFT I and the evidence for the safety is unquestioned. These are old drugs with a long history of use. At present practitioners are starting to use losartan to replace ACE inhibitors in intolerant CHF patients. The mortality effect of losartan has never been studied at all, much less proven, whereas the mortality effect of BiDil has been shown. He did not see the downside of approving the therapy and providing proper labeling for the indication, especially since the drugs are already available. He did not think this would create an unreasonable precedent.

Response

Dr. Temple said that everything we do sets a precedent. We cannot use a different standard simply because a drug is old. The data are in fact ambiguous. A marginal mortality result in V-HeFT I and near significant survival inferiority to another agent in V-HeFT II is very far below what we usually require.

Possible Subpart H Accelerated Approval

Dr. Cohn explored the possibility of approving BiDil under Subpart H. He said that if the product could receive the accelerated approval, the firm would be able to fund an add-on trial to digitalis, diuretics and ACE inhibitors. Dr. Cohn said that 50% of all heart failure patients are on a nitrate already. The combination would improve the hemodynamics, increase ETT and improve ejection fraction. He saw no down side.

Response

Dr. Temple said that if BiDil failed to show an effect in the add-on trial, it would be taken off the market. Dr. Cohn said that it still would be of benefit for CHF patients who could not take ACE inhibitors. Dr. Temple said that we would consider accelerated approval, although it was not obvious to him how that route would be viable.

Disparity of Questions at the Advisory Committee

The firm contended that the questions posed at the Advisory Committee for the BiDil application "established a different weighting for the clinical vs. statistical interpretation of the data" compared to the questions posed for the Coreg (carvedilol) application. They contended that this weighting gave the Committee less latitude to evaluate clinical benefit of BiDil than that of Coreg. While the BiDil questions were statistically oriented, the Coreg questions emphasized the clinical aspect.

Response

Dr. Temple said that the carvedilol issue was different. There was a multiplicity of data on carvedilol, with no studies suggesting a contrary outcome. The main issue there was the use of unplanned endpoints. Although he realized that Dr. Cohn felt all the data trended in the right direction for BiDil too, Dr. Temple said that the inferiority of BiDil to the positive comparator in V-HeFT II for mortality led him to doubt the mortality effect in V-HeFT I. He said that this result cannot be trivialized; it was very damaging to the application.

SUMMARY

Addressing the question of whether FDA might approve BiDil despite the Advisory Committee vote, Dr. Temple said that we go to the Advisory Committee for advice on difficult issues. Although their opinions are not binding, we do not reverse their decisions lightly. In this case we have a not approval recommendation from both the Division and the Advisory Committee. He said that he is positive that the only way that a favorable decision could result for this application would be if it were to go before the Advisory Committee again and receive their

endorsement, but that our action on the present application was likely to be a non-approval.

Minutes taken by: Gary Buehler 6/20/97

Gary Buehler

Concurrence, Chair Robert Temple 6/30/97

Robert Temple, M.D.

Orig NDA
~~HFD-110~~
HFD-110 GBuehler
HFD-110 SBenton

RD:	CGanley	5/2/97
	SChen	5/2/97
	JHung	5/17/97
	RTemple	6/16/97

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Cardiovascular Division
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March 24, 1997

Barry M. Massie, M.D.
Professor of Medicine
University of California San Francisco
V.A. Hospital (111-C)
4150 Clement Street
San Francisco, CA 94121
Fax: 415.750.6950

Dear Barry:

Our discussion about the FDA in Anaheim has left me unsatisfied. Your reticence about accepting the V-HeFT data threatens the future of Bidil. Not only do I think you have considerable influence with the Committee, but I also respect your judgment as a knowledgeable and thoughtful heart failure expert.

As a V.A. Cooperative Study, V-HeFT I and II were designed to answer scientific questions. They were not planned with regulatory considerations. After careful review of V-HeFT I by the investigators, the biostatisticians and the Operations Committee (Drs. Gorlin, Parmley, Goldberg and Knatterud) it was concluded that the favorable effect of isosorbide dinitrate-hydralazine on mortality mandated an active control for V-HeFT II. That decision is now being called into question twelve years later. I find it painful to tell these investigators that their conclusions were unjustified and their decision about V-HeFT II flawed. The expert committees from AHCPR, AHA-ACC, Canadian Heart Association and the WHO all have agreed with V-HeFT. They also should feel that their decision to recommend this therapy has been challenged. I strongly feel that the FDA has a responsibility to approve effective and safe drugs. If Bidil is effective and safe enough to be recommended for use by these committees and by the members of the Cardiorenal Committee themselves, then it should be approved. To have one standard for clinical recommendation and a different standard for drug approval is confusing to the practice community.

As a previous Chair of the Cardiorenal Committee I would have had no problem voting for approval. Charlie Ganley and, I think, Ray Lipicky also agreed that approval would have been justified. The vote for disapproval appeared to be based on some Committee-perceived rigor that is not mandated by the FDA. If one wanted to vote against the drug

because of sloppy design or conduct by the sponsor one could find a justification. But if one begins with a supportive attitude toward these landmark studies then it is easy to find the rationale for approval. I would hope the Committee began with a supportive attitude rather than with a bias against the studies.

V-HeFT I is certainly the pivotal study. A long meeting with the FDA several years ago resulted in their agreement to accept the Cox model analysis that was subsequently performed by Lloyd Fisher and by the agency. They also indicated that a $p < 0.05$ by that analysis would be adequate for FDA approval of the study. Medco decided to make the combined tablet on the basis of that meeting. We recognize that such informal decisions by the FDA are not binding, but the reversal is a serious blow to the company and to the investigators. Such reversal should be based on overwhelming new or contradictory information. Dr. Moye's rigid views that the FDA should not have accepted the Cox analysis or that the adjustments to the p-value should be several-fold may appropriately be listened to by the Committee members but I hope would not be the basis for their decision.

I don't want to bore you again with the arcane debate about p-values, but the discussion at the meeting was seriously flawed. There were only two possible comparisons identified in the protocol: 1) combined vasodilator vs. placebo; or 2) if the two vasodilator arms were different, the best treatment arm vs. placebo. The other possible comparisons were not addressed in the protocol. And there were not six primary end-points. This was a mortality trial. The two-year and overall mortality are closely correlated and these two end-points should not exact much penalty. The investigators think that even with conservative adjustment the p-value is in the 0.04–0.07 range. Why would that be a basis for disapproval? That still provides at worst a 93% confidence in the result! Even with Moye's most severe adjustment the study still would provide 90% confidence.

Does other data lend confidence to the integrity of these results? We feel they certainly do. The sequential physiologic end-point data obtained in V-HeFT is unprecedented. Peak oxygen consumption during bicycle exercise was obtained with remarkable dedication to quality control. Each test was reviewed centrally (and blindly) to assess performance and to be assured that the anaerobic threshold was surpassed. This is clearly the most reliable exercise data ever obtained in a large-scale multicenter trial. The instrumentation used in V-HeFT I was still primitive, but contemporary breath-by-breath gas exchange equipment became available by V-HeFT II and was purchased for improved end-point assessment. In addition, pilot studies of radionuclide ejection fraction were validated at each center before they were approved for participation in the trial. Such sequential ejection fraction data have never previously or subsequently been obtained in controlled trials.

The ejection fraction (which in chronic studies is probably a surrogate for ventricular volume) data track beautifully with survival in V-HeFT I. Despite all the casual statements to the contrary, there has never been a study in which chronic changes in EF and survival went in opposite directions! All the protocol-described non-mortality end-points in V-HeFT I and V-HeFT II – including peak oxygen consumption – favor isosorbide dinitrate-hydralazine: vs. placebo in V-HeFT I and vs. enalapril in V-HeFT II. The early time points for exercise performance – when the power is greater and the effect of differential mortality is not confounding – Bidil is significantly better than the comparators. No other study has ever reported long-term changes in exercise. If the drug were ineffective one would hardly expect all these end-points to support the drug in two independent trials. This is the kind of supportive data that should add credence to the mortality benefit in V-HeFT I.

You and others appear to be reluctant to accept the placebo arm in V-HeFT I. I don't know why. It is the only true placebo group (dig + diuretic) that will ever be studied. It had a robust number of deaths. It matched almost exactly the projected mortality rate. It was the same when we looked at patients randomized during the first half of the study compared to that randomized in the second half (and closer to the start of V-HeFT II). We saw no "drift." The greater benefit of enalapril vs. Bidil on mortality troubles many, but why should it? There was a greater drop-out rate with Bidil. We find a slightly greater benefit of enalapril than did other trials, probably because we excluded patients with ischemia by performing a maximum exercise test to dyspnea or fatigue, and we interdicted other dilator agents. If enalapril and nitrates work by a similar mechanism – and there is reason to think that they might – the common use of nitrates in SOLVD and the common drop-in of enalapril therapy would certainly further dilute out the benefit of randomization to enalapril. Given the homogeneity of our population and the pristine therapeutic arms it is not surprising that we can distinguish enalapril from nitrate-hydralazine on mortality.

Your stated bias against hydralazine and your feeling that there are not many patients intolerant to ACE inhibitor therapy are not really appropriate considerations in the regulatory process. Bidil should be considered on its own merits not in the context of the perceived need! Patients whose doctors will not give them an ACE inhibitor currently have no marketed alternative. Our treatment guidelines all provide one. Shouldn't the FDA follow suit?

We all would like additional studies done, particularly the addition of Bidil to an ACE inhibitor. But in the absence of an approval it is highly unlikely that these studies can be initiated. Indeed, I believe Medco would be willing to accept a "provisional" approval based on the successful completion of Phase IV trials to document efficacy. This might provide the Committee members who are not completely persuaded by the data to vote for approval without "compromising" the FDA "standards." There are certainly no safety issues to concern the Committee.

I apologize for this lengthy letter and hope you will accept it as an expansion of the discussion at the Committee meeting. I will share it with the FDA because I have no intention of trying to influence the Committee members selectively. I feel very strongly about this. These data have been the foundation of my clinical and basic research and teaching efforts for the past decade. Although I have an obvious conflict of interest, I feel that over the years I have demonstrated my dedication to objectivity and balance. I feel confident that that is the case here as well.

Your thoughts on these issues and on a "provisional" approval would be greatly appreciated.

Sincerely,

Jay N. Cohn, M.D.
Professor of Medicine

JNC:ncl
cc: Raymond Lipicky, M.D.
Robert Temple, M.D.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: MAR 4 1997

FROM: Joan C. Standaert, Executive Secretary
Cardiovascular and Renal Drugs Advisory Committee

SUBJECT: 80th Meeting of the Cardiovascular and Renal Drugs Advisory Committee, February 27-28, 1997: INFORMATION ALERT MEMORANDUM

TO: Director, Center for Drug Evaluation and Research, HFD-1

Meeting in open session, the committee deliberated on four NDA applications. The first was NDA 20-727, BiDil, a fixed dose combination of hydralazine and isosorbide dinitrate for the treatment of congestive heart failure. The application presented two studies in support of the proposed indication, V-HeFT I (vs placebo) and V-HeFT II (vs enalapril). Both studies had six "major" endpoints; the primary endpoint for both was effect on mortality.

The committee unanimously recommended that there was no statistically significant effect on mortality for V-HeFT I at 6 months or over the entire study and 12-no, 1-abstention, that an effect on hospitalizations was demonstrated. BiDil was not superior to enalapril in V-HeFT II and possible comparison with placebo was unknown. They recommended 9-no, 3-yes, that BiDil not be approved for use in congestive heart failure.

NDA 20-297/S-001, Coreg, carvedilol, for use in congestive heart failure was considered by the advisory committee for a second time. Additional data from study 223, the Australian study, was presented. The committee unanimously recommended, as previously, that study 240 was significant for primary endpoints of mortality and hospitalization and maintained significance after adjustment for the medications component.

While study 223 did not achieve significance for the three pre-specified endpoints, it did provide supportive evidence for efficacy. Taken in context with data from other multicenter studies, reanalyzed by the sponsor, the committee recommended 8-yes, 2-no, that carvedilol be approved for use in congestive heart failure.

NDA 20-689, Posicor, mibefradil, applied for use of the drug in hypertension and angina. A chief safety concern was mibefradil associated repolarization changes seen in human electrocardiograms. The nature and significance of these changes was discussed at length. They appear to be a hitherto-unreported phenomenon, although one that in hindsight is also seen with verapamil and diltiazem. The electrocardiographic repolarization changes resemble those seen

with bepridil, sotalol, and other drugs known occasionally to cause polymorphic ventricular tachycardia. Unlike these other drugs, mibefradil did not prolong the action potential in *in vitro* tests, did not elicit ventricular arrhythmias in animal models, and was not credibly associated with arrhythmias in the clinical database.

The committee recommended 5-yes, 3-no, that mibefradil be approved for use in hypertension and angina, at doses of 50-100 mg. The committee recommended that the mibefradil labeling carry the usual calcium channel blocker warning about use in patients with LV dysfunction. Also, the committee recommended that the label include appropriate warnings about coadministration of mibefradil with drugs (cyclosporine, quinidine, astemizole, etc.) whose metabolism is dependent on the P450 (3A4) PATHWAY.

Integrilin, intrifiban, NDA 20-718, requested approval as adjunctive therapy in patients undergoing percutaneous transluminal angioplasty (PTCA) and for prevention of acute cardiac ischemic complications related to abrupt closure. Support for the indication was based mainly on the results of a single, large clinical trial IMPACT II. The primary endpoint was death, AMI or urgent intervention at 30 days from randomization.

The committee recommended 6-yes, 2-no, that this trial achieved statistical significance for its prespecified endpoint. They unanimously recommended that this trial was not significantly persuasive to support approval of the drug for its proposed indications.

/S/

Joan Standaert

Distribution:

HFD-2 Deputy Director for Review Management
HFD-3 Deputy Director for Pharmaceutical Science
HFD-4 Associate Director for Medical Policy
HFD-5 Associate Director for Policy
HFD-6 Executive Operations Staff
HFD-7 Regulatory Affairs Staff
HFD-21 Advisors and Consultants Staff
HFD-21 M. Brooks, Advisors and Consultants Staff
HFD-101 Director, Office of Drug Evaluation I
HFD-101 Special Assistant, ODE I
HFD-110 Director, Division of Cardio-Renal Drug Products
HFD-110 Executive Secretary of Cardio-Renal Drug Advisory Committee
HFD-120 Director, Division of Neuropharmacological Drug Products
HFD-150 Director, Division of Oncologic Drug Products
HFD-102 Director, Office of Drug Evaluation II
HFD-510 Director, Division of Metabolism and Endocrine Drug Products
HFD-570 Director, Division of Pulmonary Drug Products
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HFD-160 Division of Medical Imaging and Radiopharmaceutical Drug Products
HFD-170 Director, Division of Anesthesiology, Critical Care and Addiction Drug Products
HFD-180 Director, Division of Gastrointestinal and Coagulation Drug Products
HFD-104 Director, Office of Drug Evaluation IV
HFD-520 Director, Division of Anti-Infective Drug Products
HFD-530 Director, Division of Anti-Viral Drug Products
HFD-105 Director, Office of Drug Evaluation V
HFD-540 Director, Division of Dermatologic and Ophthalmologic Drug Products
HFD-550 Director, Division of Anti-Inflammatory, Analgesic and Dental Drug Products
HFD-560 Director, Division of OTC Drug Products
HFD-300 Director, Office of Compliance
HFD-600 Director, Office of Generic Drugs
HFD-700 Director, Office of Epidemiology & Biostatistics
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HFD-850 Director, Office of Clinical Pharmacology & Biopharmaceutics
HFD-900 Director, Office of Testing & Research
HF-35 Director, Orphan Products Development
HFE-40 Policy Analysis Staff
GCF-1 General Counsel
HFA-224 Records Retrieval Unit

Questions

BiDil® for
heart failure
27 February 1997

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Cardio-Renal Advisory Committee

The Advisory Committee is asked to consider the approval of BiDil®, a fixed-dose combination of hydralazine and isosorbide dinitrate (ISDN), in the treatment of congestive heart failure. The to-be-marketed formulations of BiDil contain hydralazine/ISDN doses of 37.5/10, 37.5/20, 75/20, and 75/40 mg.

The two studies that support the use of hydralazine and ISDN in the treatment of congestive heart failure were performed by Dr. Jay Cohn and the V.A. Cooperative Study Group. V-HeFT I was a pioneering trial that influenced the design of modern heart failure trials. Placebo-controlled V-HeFT I began enrollment in 1980 and was terminated because of curtailment of funding. V-HeFT II ran from 1986 to 1991 and compared enalapril with hydralazine plus ISDN.

Both hydralazine and ISDN are approved and marketed drugs. Ordinarily, the approval of the fixed-dose combination product would require evidence that both drugs contribute to the therapeutic effect. There are no such data for BiDil. When such a situation has arisen, the Agency has said it would consider approval if there were compelling evidence that the combination favorably affected some irreversible end point, like mortality. The Division would, however, like the Committee to consider the following concerns:

- **Multiplicity:** The V-HeFT studies each had 6 "major" end points, but the studies were sized to detect an effect on mortality, and the protocols fairly clearly indicated that the primary objective was to study the effects of hydralazine and ISDN on mortality. Both studies also listed cardiovascular hospitalization as another "major" end point, and both studies measured maximum oxygen consumption during treadmill exercise and other indices of exercise capacity.
- **Bioequivalence:** The formulations of hydralazine and ISDN were not bioequivalent between the V-HeFT I and II studies, and the BiDil formulation is not bioequivalent to that used in either study.
- **Tolerance:** During repetitive dosing in patients with chronic stable angina, nitrate administration without a 12-hour nitrate-free interval ordinarily leads to tolerance.

V-HeFT I

1. Factors that might affect interpretation of the mortality results include the following:

- There were 4 interim analyses, conducted by O'Brien/Fleming rules.
- The protocol outlined three possible comparisons in the primary analysis using the log-rank test. The comparisons included (1) each active treatment arm to each other, (2) the combined vasodilator arms to placebo, and (3) each active treatment arm to placebo. Each of these analyses was performed at least once during the course of the study.
- There were two other analyses, (1) a protocol-specified Cox regression, intended to identify covariates that were important, and (2) a retrospective Cox regression analysis (placebo vs. hydralazine-ISDN) using baseline covariates specified by the Division. The Cox regression analyses require the somewhat arbitrary imputation of values for missing baseline covariates.
- Mortality was specified to be evaluated as either total mortality over the duration of the study or as two-year mortality.

The published description of the study and the NDA submission reported nominal *p*-values. In interpreting the *p*-values for mortality analyses in V-HeFT I, by what factor, if any, should the nominal *p*-value be inflated for...

1.1. ...multiple primary end points?

1.2. ...multiple interim analyses?

1.3. ...multiple treatment-arm-to-treatment-arm and pooled-to-control comparisons?

1.4. ...multiple statistical test methods?

1.5. ...multiple durations for assessment?

2. What is the appropriate factor for the overall adjustment of the nominal *p*-value for mortality in V-HeFT I?

3. In the Cox regression analysis of mortality in V-HeFT I, what is the appropriate method for imputing values for missing baseline covariates?

4. Was there a statistically significant effect found in V-HeFT I for...

4.1. ...mortality during the entire study period?

4.2. ...2-year mortality?

5. Was there a statistically significant effect found for hospitalizations for cardiovascular causes in V-HeFT I?

6. There were 3 measures of exercise tolerance in V-HeFT I. For which of these were there statistically significant treatment effects?

- Maximum oxygen consumption at peak exercise during a maximal exercise tolerance test.
- Total duration of symptom-limited exercise for a maximal exercise tolerance test.
- Submaximal exercise duration.

7. Was there a statistically significant effect found for Quality of Life in V-HeFT I?

8. Was there a statistically significant effect found for left ventricular ejection fraction in V-HeFT I?

9. Are the effects on headache and blood pressure in V-HeFT I consistent with the development of tolerance to isosorbide dinitrate?

V-HeFT II

V-HeFT II had no placebo control group. The Division and the Advisory Committee have held that a successful active comparator trial requires one to conclude

- that the new treatment would have beaten placebo, had there been a placebo group, and
- that the estimated effect size of the new treatment is not less than half of the effect size for the comparator agent.

10. One way in which it could be concluded that hydralazine-ISDN was superior to placebo would be if the combination were superior to enalapril in V-HeFT II. Was hydralazine-ISDN superior to enalapril for any of the mortality or exercise end points?

11. If hydralazine-ISDN was not superior to enalapril, it might still be superior to placebo.

11.1. The sponsor argues that an answer to that question would be best derived by comparing the hydralazine-ISDN group to the placebo group in V-HeFT I. The Division argues that the best comparison would be with the results of SOLVD Treatment (where the magnitude of treatment effect of enalapril was demonstrated) or with a combination of the results of SOLVD Treatment and V-HeFT I. What is the appropriate placebo group for comparison?

11.2. Had placebo been present, is it likely that the effect of hydralazine-ISDN would have been greater than that of placebo?

11.3. How does one show that a new treatment has at least half of the effect size of an active comparator? Does this mean...

11.3.1. ...that the point estimate of effect size is at least half as great?

11.3.2. ...that the confidence limits exclude an effect half as great?

11.4. Was the effect of hydralazine-ISDN at least half that of enalapril?

11.5. Like V-HeFT I, V-HeFT II had multiple end points, multiple time points (2 and 5 years) for evaluation of mortality, and interim analyses. What is the appropriate adjustment to the nominal *p*-value for multiple end points and comparisons, and for interim analyses?

12. Do the mortality results of V-HeFT II confirm the findings of V-HeFT I?

13. Exercise capacity was measured by maximum oxygen consumption at peak exercise and total duration of maximum exercise. Results of both measures of exercise capacity, in both the Division's and sponsor's view, gave similar results. One analysis of exercise duration included only those subjects who stopped exercise (post-randomization) for dyspnea or fatigue.

13.1. Should this be the pivotal analysis for determining whether there was a treatment effect on exercise capacity?

13.2. By the appropriate analysis, was there a statistically significant treatment effect on exercise duration?

13.3. For maximum oxygen consumption at peak exercise, was there a statistically significant treatment effect, favoring hydralazine-ISDN?

14. With regard to hospitalizations for cardiovascular causes...

14.1. ...was there a statistically significant effect, favoring hydralazine-ISDN?

14.2. If not, are the data supportive of some related benefit of hydralazine-ISDN?

15. Was there a statistically significant treatment effect on ejection fraction, favoring hydralazine-ISDN?

16. How compelling is the evidence that hydralazine prevents the occurrence of tolerance to ISDN?

17. If the combination product were to be approved, ...

17.1. ...what are the appropriate dosing interval and instructions for titration of dose?

17.2. ...what are the specific benefits of treatment to be named in the label?

17.3. ...should use be restricted to patients who cannot tolerate ACE inhibitors?

17.4. ...should it be for use with an ACE inhibitor?

18. Should *BiDil* be approved for use in the treatment of congestive heart failure?

6 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(5) Deliberative Process

____ § 552(b)(4) Draft Labeling

OFFICES OF DRUG EVALUATION
ORIGINAL NDA/NDA EFFICACY SUPPLEMENT
ACTION PACKAGE CHECKLIST

NDA # 20-727 Drug: BiDil (Hydralazine HCl & ISDN) Tablets

Applicant: Medco Research Chem/Ther/other Types: 45

CSO/PM: Buehler Phone: 594-5332 HFD- 110

USER FEE GOAL DATE: 7/3/97 DATE CHECKLIST COMPLETED: 4/11/97

Arrange package in the following order (include a completed copy of this CHECKLIST): — Check or Comment

1. ACTION LETTER with supervisory signatures — AP ____ AE ____ NA X
   Are there any Phase 4 commitments? — Yes ____ No ____
2. Have all disciplines completed their reviews? — Yes X No ____
   If no, what review(s) is/are still in draft?
3. LABELING (package insert and carton and container labels). — Draft X / Revised Draft ____ / Final ____
   (If final or revised draft, include copy of previous version with ODE's comments and state where in action package the Division's review is located. If Rx-to-OTC switch, include current Rx Package insert and HFD-312 and HFD-560 reviews of OTC labeling.)
4. PATENT INFORMATION — X
5. EXCLUSIVITY CHECKLIST — NA
6. PEDIATRIC PAGE (all NDAs) — X
7. DEBARMENT CERTIFICATION (Copy of applicant's certification for all NDAs submitted on or after June 1, 1992). — X
8. Statement on status of DSI's AUDIT OF PIVOTAL CLINICAL STUDIES — not requested
   If AE or AP ltr, explain if not satisfactorily completed. Attach a COMIS printout of DSI status.
   If no audits were requested, include a memo expaining why.
9. REVIEWS & MEMORANDA:

DIVISION DIRECTOR'S MEMO	If more than 1 review for any	X
GROUP LEADER'S MEMO	1 discipline, separate reviews	No
MEDICAL REVIEW	with a sheet of colored paper.	X
SAFETY UPDATE REVIEW	Any conflicts between reviews	NA (combined)
STATISTICAL REVIEW	must have resolution documented	X (combined)
BIOPHARMACEUTICS REVIEW		X
PHARMACOLOGY REVIEW (Include pertinent IND reviews)		X
Statistical Review of Carcinogenicity Study(ies)		NA
CAC Report/Minutes		[illegible]
CHEMISTRY REVIEW		X
Labeling and Nomenclature Committee Review Memorandum		X
Date EER completed not compl (attach signed form or CIRTS printout)		OK ____ No ____
FUR needed ____ FUR requested ____		
Have the methods been validated?		Yes (attach) ____ No X
Environmental Assessment Review / FONSI		Review X FONSI X
MICROBIOLOGY REVIEW		NA
What is the status of the monograph?		

10. CORRESPONDENCE, MEMORANDA OF TELECONS, and FAXes — ✓
11. MINUTES OF MEETINGS
    Date of End-of-Phase 2 Meeting: 11/20/92
    Date of pre-NDA Meeting: None
12. ADVISORY COMMITTEE MEETING MINUTES — Minutes ____ Info Alert ✓
    or, if not available, 48-Hour Info Alert or pertinent section of transcript. — Transcript ____ No mtg ____
13. FEDERAL REGISTER NOTICES; OTC or DESI DOCUMENTS — NA
14. If approval letter, has ADVERTISING MATERIAL been reviewed? — Yes NA No ____
    If no and this is an AP with draft labeling letter, has advertising material already been requested? — Yes, documentation attached ____ / No, included in AP ltr ____
15. INTEGRATED SUMMARY OF EFFECTIVENESS (from NDA) — ✓
16. INTEGRATED SUMMARY OF SAFETY (from NDA) — ✓

revision: 5/14/96

APPLICATION SUMMARY

NDA 20-727 BiDil (hydralazine HCL and isosorbide dinitrate) Tablets, 37.5/10, 37.5/20, 75/20, 75/40 mg

Sponsor: Medco Research

Date of Submission: July 3, 1996

User Fee Date: July 3, 1997

BACKGROUND

This application uses the V-HeFT I and V-HeFT II trials as pivotal studies as support for the indication of treatment of congestive heart failure as an adjunct to standard therapy (dig. and diuretics) in patients who are intolerant or have a contraindication to ACE inhibitors. They claim that the therapy improves survival and exercise tolerance.

A pre-IND meeting was held for this combination product on November 5, 1992. During that meeting, Dr. Lipicky discussed the issues that would have to be addressed in an NDA submission for the product. The minutes of that meeting are appended to this document.

REVIEW TEAM

Medical - Dr. Ganley - V-HeFT I Secondary - Dr. Lipicky
Dr. Chen - V-HeFT II
Statistical - Dr. Hung

A combined medical/statistical review was completed by Drs. Ganley, Chen and Hung. The review highlighted the issues raised by the two trials. An approvability recommendation, however, was not made.

Biopharm. - Dr. Marroum

Dr. Marroum made numerous comments in his review, the most critical of which are:

1. In view of the fact that the 37.5/10 mg tablet showed a slower dissolution performance compared to the 37.5/20, 75/20 and 75/40 mg tablets in all 4 media tested, an in-vivo bioavailability waiver cannot be granted for the two middle strengths (37.5/20, 75/20 mg). The multiple-dose study that the firm is currently conducting using all strengths in CHF patients, however, could provide the necessary data.

2. When asked to provide the pharmacokinetic parameters for study CB02 in electronic form on diskette, the only data submitted was for the normalized parameters to a weight of 65 kg. Upon review, it was discovered that the data on diskette did not match the data found in the NDA, and the discrepancy remains unexplained.

3. The firm's proposal for inclusion of information regarding food-effect of hydralazine and

isosorbide dinitrate based on published literature cannot be accepted. The firm would be required to do a food-effect study on the to-be-marketed formulation of BiDil to make a statement in labeling regarding the effect of administration of food on the absorption of BiDil.

Pharmacology - Dr. Belair

No original animal studies were done for this application. The firm has done a literature/FOI review of available data on hydralazine and ISDN and submitted it to the NDA.

Chemistry - Dr. Advani EER - Submitted 7/26/96

The EIR has not been completed.

The firm still has not adequately addressed the possibility of an interaction between the drug substances to form N-nitrosoamines, products that have the potential to be carcinogenic.

Based on analytical results, the NDA method does not appear suitable for regulatory control of the product. One extra large peak was found in method [ ] that was not identified, and the [ ] for the compound are significantly different from the one shown in the method. Also, the product did not meet the firm's specifications for impurities of NMT [ ] Impurity amounts in the four lots tested were [ ]

Environmental Assessment - Dr. Zielinski

The EA was acceptable.

DSI - Dr. El Hage

Dr. Lipicky decided that clinical trial inspections will not be required for the V-HeFT I and II trials.

Advisory Committee

On February 27, 1997, the Advisory Committee voted 8-3 to not approve BiDil for a mortality claim in patients with CHF who cannot take ACE inhibitors.

4/18/97

Gary Buehler
Regulatory Health Project Manager

Orig NDA
HFD-110
HFD-110 GBuehler
HFD-110 SBenton

Kaufler

JAN 1 5 1997

MEETING MINUTES

Date: December 19, 1996 9:00 AM CR "F" WOC II

Subj: NDA 20-727 BiDil (Hydralazine HCl and Isosorbide Dinitrate) Tablets
Pre-Advisory Committee Meeting

Meeting Chair: Raymond Lipicky, M.D.

Recorder: Gary Buehler

Medco Attendees:

Janice Parry, Pharm. D.	Manager, Regulatory Affairs
Joseph Quinn	Director, BioStatistics and Data Management
Mary Dixon	Senior Project Manager
J. N. Cohn, M.D.	Consultant, Principal Clinical Investigator
Keith Schneider	Director, Regulatory Affairs
Donald A. Knight	[ ] Regulatory Affairs
Mary Lou Schenck	[ ] Regulatory Affairs

FDA Attendees:

Raymond Lipicky, M.D.	Dir., Div. of Cardio-Renal Drug Prod., HFD-110
Robert R. Fenichel, M.D., Ph.D.	Deputy Director, HFD-110
Shaw Chen, M.D., Ph.D.	Supervisory Medical Officer, HFD-110
Charles Ganley, M.D.	Supv. Medical Officer, Application MO, HFD-110
James Hung, Ph.D.	Statistical Reviewer, HFD-110
Gary Buehler	Project Manager, HFD-110

BACKGROUND

Dr. Lipicky asked the firm to meet again to get an update for the upcoming Advisory Committee meeting on February 27-28, 1997. The firm prepared the following agenda for the meeting:

1. Status of the review of the application.
2. Outstanding issues for the review.
3. Minutes from the Data and Safety Committee requested by Dr. Ganley.
4. Results of the statistical analyses of V-HeFT I.
5. Issues for the Advisory Committee.

DISCUSSION/DECISIONS

1. Status of the Review.

Dr. Ganley said that he had completed the mortality analysis and he is finishing the exercise analysis for V-HeFT I. He only plans to do an exercise, mortality and possibly hospitalizations for V-HeFT II. He has not reached a conclusion yet.

Dr. Hung said that he did an analysis to check for robustness of the p value for martality in V-HeFT I. He found that the p value can range from 0.1 to 0.01 depending on what values are imputed for the missing data. He said that Dr. Fisher used a regression model to estimate the missing values.

Dr. Ganley noted that while the ETT data were not impressive in V-HeFT I, it looks like there is something there (p=0.08). Hospitalizations also go in the right direction, although they too do not achieve statistical significance. Mr. Clark said that the equipment used in V-HeFT I to measure oxygen consumption was very antiquated. He thought that this could explain the disappointing results.

Dr. Ganley said that the analysis of the V-HeFT II trial was less complicated. He hopes to have the review completed by mid-January.

2. Outstanding Issues form the Review

Drs. Ganley and Hung said that they have not identified any new issues from the review.

3. Minutes from the Data and Safety Committee

The firm stated that they are attempting to get the minutes from the Data and Safety Committee meeting from the V-HeFT I trial. They said that they hope to have them soon.

4. Results of Additional Statistical Analyses of V-HeFT I.

Mr. Clark said that both the V-HeFT I and II trials had to be stopped prematurely due to funding problems. They therefor did not have sufficient power for their planned analyses. This explains the lack of statistical significance using the log rank test.

Since the V-HeFT II trial did not have a placebo group, the firm has compared the results of the trial to the placebo group in V-HeFT I. Dr. Ganley said that the enalapril group of the V-HeFT II trial must also be compared to the same placebo group. Dr. Lipicky said that the placebo group from the CONSENSUS or SOLVD Treatment studies would also be needed. Despite the discussion, no one really thought that this type of analysis, using the placebo group from another study, would be appropriate.

Dr. Ganley thought that the major issue would be why the log rank test is not appropriate. Dr. Hung said that one must keep in mind that all of the analyses except the logrank test are post hoc, and that one is more likely to pick the best one in this circumstance. Dr. Cohn said that he thought that the Agency had agreed to accept the variables chosen by Dr. Packer for the analysis.

5. Advisory Committee Meeting

Dr. Lipicky said that the time frames discussed at the November meeting for when written material needs to be sent to the AC members are the same. He said that we would like to review the firm's package, but we would review the document within 24 hours.

Dr. Lipicky said that because of recent developments that could result in another application being taken to the Advisory Committee, their presentations will have to be brief.

As what the issues for discussion will be at the Advisory Committee, Drs. Lipicky and Ganley mentioned the following:

1. Patient compliance in the V-HeFT I Trial.
2. Tolerance to ISDN given QID.
3. Contribution of each ingredient (no single entity arms in the study).
4. Two trials (we have one placebo-controlled and one positive-controlled trial)
5. Correct Dose?
6. For whom? (patients who were studied were not intolerant to ACE inhibitors)
7. Women? (there were no women in the clinical trials)

SUMMARY

The discussions were summarized. It was decided that if any additional issues arise between now ant the middle of January, the reviewers will contact Medco. If Medco believes that a meeting is needed to address these additional issues, one will be scheduled.

Minutes taken by: Gary Buehler 1/15/97

Gary Buehler

Concurrence, Chair Lipicky 1/22/97

Raymond Lipicky, M.D.

Orig NDA
HFD-110
HFD-110 GBuehler
HFD-110 SBenton

RD:	CGanley	1/10/97
	JHung	1/10/97
	SChen	1/13/97

MEDCO RESEARCH, INC.

DUPLICATE

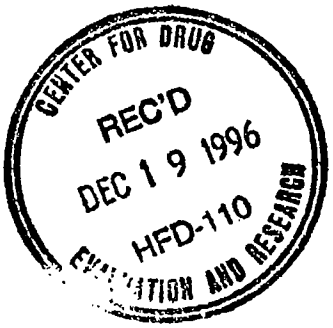
I think that "BiDil" is fine. We will not follow the LVE's recommendation on this one.
R F 11/10/97

NEW CORRESP (NC)

December 18, 1996

RESPONSE TO REVIEWERS

Raymond J. Lipicky, M.D.
Director, Division of Cardio-Renal Drug Products
CDER, ODE I, WOC 2, HFD-110, Rm. 5309
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852



REF: NDA 20-727
BiDil® (hydralazine HCl/isosorbide dinitrate) Tablets

Dear Dr. Lipicky,

Reference is made to a telephone conversation with the Division on October 30, 1996, in which Medco Research was informed that there was concern that the name of our product, BiDil®, was misleading, in that the name might imply that the product should be taken twice a day (BID).

The choice of the brand name BiDil® was made by Medco Research in order to attract attention to the nature of the product, the combination of two (Bi) vasodilators (Dil), hydralazine HCl and isosorbide dinitrate. We feel that it is unlikely that the name itself would lead to confusion regarding administration for two reasons: 1) the product will be dispensed by pharmacists, who will be able to intepret the prescriber's instructions to take the product four times a day (QID), and these instructions will be transmitted to the patient in the form of the dispensing label; and, 2) the product will be taken by a lay public, who will be unlikely to interpret BiD (the portion of the name purported to denote "BID") as "twice a day".

Additionally, the name "BiDil" is a registered trademark, implying a unique name and logo. No concerns were raised by any of the investigators involved with BiDil®'s development about potential misinterpretation of the brand name. Indeed, other products are presently marketed with brand names that could potentially pose a similar risk of confusion. These include, but are not limited to Tridil (an antianginal for continous infusion), Triacet (a corticosteroid to be administered BID or QID), Uni-Ace (an analgesic to be administered Q4-6H), etc.

P.O. BOX 13886 • RESEARCH TRIANGLE PARK, NC 27709 • PHONE: (919) 549-8117 • FAX: (919) 549-7515

Consult #661 (HFD-110)

BiDIL hydralazine hydrochloride and isosorbide dinitrate

The Committee found no look-alike/sound-alike conflicts with any existing proprietary name. However, it is the practice of the Committee to find a proprietary name unacceptable if it contains a common medical abbreviation in a misleading manner. The proposed proprietary name BIDIL, a two component product, contains BID which is an abbreviation for the Latin instruction of "twice daily". Although the proposed name is presented to emphasize the Bi (meaning two) aspect of the name, the Committee feels it could be potentially misleading and confusing by using BiD in the name.

The LNC finds the proposed proprietary name unacceptable.

DLBowing 10/1/96, Chair
CDER Labeling and Nomenclature Committee

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-727

1996
21

Medco Research, Inc.
Attention: Janice L. Parry, Pharm.D.
P.O. Box 13886
Research Triangle Park, NC 27709

Dear Dr. Parry:

Please refer to your pending July 3, 1996 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for BiDil (hydralazine HCl and isosorbide dinitrate) Tablets.

We also refer to your amendment dated September 26, 1996.

We have completed our review of the manufacturing and controls section of your submission and have identified the following deficiencies:

1. There is a possibility of interaction between the drug substances to form N-nitrosoamines, and these possible products are carcinogenic. We, therefore, suggest you also test tablets from several of your oldest batches, at lower than the [ ] levels the related compounds formed on accelerated and room temperature storage conditions. We recommend you use state of the art separation methods to detect these impurities where the limit of detection is in the ppm range. Identify and study the pharmacology and toxicity of these compounds if found.

2. Your data on thermal stress study of the HPLC method indicate approximately [ ] degradation of drug products. We suggest you identify and evaluate these degraded compounds. We may have additional comments after our district laboratories have completed the work on your methods validation.

3. Stability tables on pages 18 and 19 for batch DG29B tablets erroneously mention the storage condition in [ ] bottles. Also the tablet dosage for batches DG30A and DG30B shown as [ ] should be [ ] (pages 20-23). Please correct these pages of attachment VI of your submission.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact:

Mr. Gary Buehler
Regulatory Health Project Manager
(301) 594-5332

Sincerely yours,

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

cc:
Original NDA
HFD-110
HFD-110/GBuehler/11/12/96;11/10/96
sb/11/15/96;11/19/96
R/D: JAdvani/11/18/96
RWolters/11/19/96
NMorgenstern/11/19/96

INFORMATION REQUEST

Buehler

MEETING MINUTES

DEC 9 1996

Date: November 21, 1996 9:00 AM CR "H" WOC II

Subj: NDA 20-727 Bidil (hydralazine HCl and isosorbide dinitrate) Tablets
Pre-Advisory Committee Meeting

Sponsor: Medco Research
Research Triangle Park, NC

Meeting Chair: Raymond Lipicky, M.D.
Sponsor Chair: Jay Cohn, M.D.
Recorder: Gary Buehler

Medco Attendees:

Cesare Orlandi, M.D.	VP, Research and Development
Janice Parry, Pharm. D.	Manager, Regulatory Affairs
Joseph Quinn	Director, Biostatistics and Data Management
Mary Dixon	Senior Project Manager
Jay Cohn, M.D.	Principal Clinical Investigator
Lloyd Fisher, Ph.D.	Consultant Statistician
Donald Knight	Regulatory Affairs
Mary Lou Schenck	Regulatory Affairs

FDA Attendees:

Raymond Lipicky, M.D.	Dir., Div. of Cardio-Renal Drug Prod., HFD-110
Robt R. Fenichel, M.D., Ph.D.	Deputy Director, HFD-110
Charles Ganley, M.D.	Supervisory Medical Officer, HFD-110
Shaw Chen, M.D., Ph.D.	Supervisory Medical Officer, HFD-110
James Hung, Ph.D.	Statistician, HFD-710
Kooros Mahjob, Ph.D.	Acting Statistical Team Leader, HFD-710
Gary Buehler	Project Manager, HFD-111
Zelda McDonald	Project Manager, HFD-111
Steve Caras, M.D.	New Staff
Khin U, M.D.	New Staff
Femi Williams, M.D.	New Staff
Isaac Hammond, M.D., Ph.D.	New Staff

BACKGROUND

NDA 20-727 for Bidil (hydralazine HCl and Isosorbide Dinitrate) Tablets was submitted to the Division of Cardio-Renal Drug Products on July 3, 1996. Primary efficacy support for the application was provided by the V-HeFT I and II trials. The proposed indication was to provide a mortality benefit in patients who were intolerant or could not take ACE inhibitors.

AGENDA

Dr. Lipicky asked the firm to meet to discuss their preparation and presentation for an upcoming Advisory Committee Meeting on February 27-28, 1997.

DISCUSSION POINTS

Structure of Advisory Committee Meeting

Dr. Lipicky outlined the procedures to be followed when a drug is taken to the Cardio-Renal Drugs Advisory Committee. He said that all written material should be sent to the Advisory Committee at least one month before the meeting. In general, nothing is discussed at the meeting that has not been submitted in writing ahead of the meeting. The committee members will also receive copies of the FDA reviews, but there will be no formal presentation by FDA reviewers.

The Advisory Committee members may have questions about the written submissions. They cannot communicate directly with sponsors, but material can be mailed directly to them.

The sponsor should provide a summary of the application to the advisory committee members. This may be the integrated summary of safety and efficacy, or it may be a different document drafted expressly for this purpose. This document should be submitted to the Division for clearance before it is sent to the advisory committee members.

Questions will be prepared by the Division. The final questions will not be ready until the day of the meeting, but drafts will be available 1-2 weeks before the meeting. We will provide the sponsor with a copy of the draft questions as soon as it is available.

Issues for Discussion at the Meeting

1. Statistical analysis of the V-HeFT I trial.

Dr. Cohn said that he did not believe that the analysis of the V-HeFT I trial using the covariates suggested by Dr. Packer would be an issue. Dr. Lipicky said that whenever an analysis is used that is not pre-specified, the result is an issue. If this analysis is accepted, a decision will also have to be made as to how much statistical penalty should be assessed. The question of accepting a single trial for the mortality claim was also discussed. Dr. Cohn again stated that he did not believe that this would be an issue, but Dr. Lipicky disagreed.

2. Value of the V-HeFT II Trial

The V-HeFT II trial was not placebo controlled, and it did not beat the positive control (enalapril) used for mortality. It did, however, show some symptomatic benefit compared to enalapril.

3. Tolerance

The firm was instructed to prepare a full explanation, with references, as to why tolerance does not occur to the effect of isosorbide dinitrate given QID. They can bring consultants to the meeting to assist in the presentation or answer questions.

4. Data and Safety Monitoring Board (DSMB)

Dr. Ganley said that they should be prepared to explain how the DSMB monitored the study. He said that the documentation relating to the study being stopped should be available.

ACTION ITEMS

Dr. Lipicky said that the firm should meet with the Division before Christmas to discuss the major issues again. At that time we should be able to determine on what issues there is disagreement.

Recorder:_____
Gary Buehler

Concurrence, Chair_____
Raymond Lipicky, M.D.

Orig NDA
HFD-110
HFD-110 GBuehler
HFD-110 SBenton
RD: CGanley 12/2/96
JHung 12/4/96

BUEHLER

MINUTES OF A TELEPHONE CONFERENCE

NOV 8 1996

Date: November 6, 1996

Subj: NDA 20-727 BiDil (isosorbide dinitrate and hydralazine HCl) Tablets

Sponsor: Medco Research

Meeting Chair: Raymond Lipicky, M.D.
Recorder: Gary Buehler
Sponsor Lead: Cesare Orlandi, M.D.

Medco Attendees:

Roger Blevins, Pharm D.	Medical
Cesare Orlandi, M.D.	Medical
Janice Parry, Pharm D.	Regulatory
Joe Quinn	Biostatistics

Medco Consultants

[ ]	[ ]
[ ]	[ ]
Jay Cohn, M.D.	U. of Minnesota

FDA attendees

Raymond Lipicky, M.D.	Dir., Div. of Cardio-Renal Drug Products, HFD-110
Charles Ganley, M.D.	Supervisory Medical Officer, HFD-110
Patrick Marroum, Ph.D.	Team Leader, Div. of Pharm. Science I, HFD-860
Gary Buehler	Project Manager, HFD-111

BACKGROUND

Medco submitted the NDA for BiDil on July 3, 1996. Before submission of their NDA, the firm had meetings with Division personnel to determine what would be required for the application. At a meeting held with the Biopharmaceutics reviewers, they were informed that a multiple-dose study would be required to describe the pharmacokinetic characteristics of their formulation due to the fact that the bio study that they performed to link the clinical formulation with the to-be-marketed BiDil formulation was done using a single-dose design. Because of the non-linear nature of the pharmacokinetics of hydralazine and ISDN, however, it is difficult to extrapolate the results of the study to a multiple-dose setting. They were, therefore, contacted by Dr. Marroum and informed that they would also have to do a multiple-dose trial to describe the characteristics of their formulation (this was done after consultation with Dr. Lipicky). They were also informed, however, that the study would not have to be submitted with their NDA, but the results would have to be submitted before any approval action. The firm submitted the protocol for the trial on August 9, 1996. Dr. Marroum completed his review of the protocol on August 21, 1996. On September 10, 1996, a telephone conference was held with Medco, their [ ] consultants and Drs. Ganley and Marroum. The issues relating to the need for the pharmacokinetic study and its design were discussed, but the firm was informed that the final word would have to wait for Dr. Lipicky's input.

On September 12, 1996 the issues were presented to Dr. Lipicky by Drs. Marroum and Ganley. Dr. Lipicky said that we should have descriptive kinetics on the formulation, and ideally they

should be in CHF patients and include the entire dosing range. He said that he understood the firm's reluctance to do a multiple dose study in volunteers at the highest dose. He could not, however, see why there would be a problem in CHF patients since they are the patients expected to take the drug. He suggested that they do the trial in CHF patients. They should start dosing with the lowest dose. When steady state is reached, they should titrate up to the next highest dose and give it until steady state is reached. They should do this until the entire range is covered. Dr. Marroum said that steady state is reached after 5 doses. Dr. Lipicky said that all patients may not be able to tolerate the highest doses. If so, they will drop out at the highest dose tolerated. This study will enable us to collect descriptive pharmacokinetics at each dose at steady state and also assess the tolerability of the formulation in CHF patients.

DISCUSSION POINTS/DECISIONS

Pharmacokinetic Study

Dr. Lipicky said that the problem is that the to-be-marketed formulation is not bioequivalent to either formulation used in the clinical trials (V-HeFT I or II). We would like to see some multiple-dose descriptive pharmacokinetics in patients with congestive heart failure. The number of patients need only be 10-12. He again described the dose escalation design that is outlined above. Dr. Lipicky said that the patients can be on background ACE inhibitors and stated that we are not looking for bioequivalence; we just want a description of the kinetic behavior of the formulation.

Medco said that they thought that they could conduct the study as described.

Tradename

The firm was informed that the Labeling and Nomenclature Committee had found the tradename BiDil unacceptable, because it contains the common medical abbreviation, BID. The committee believed that this could be potentially misleading and confusing.

Dr. Lipicky relayed the committee's reasons to Medco. Dr. Cohn suggested putting a hyphen between BI and Dil, but Mr. Buehler said that the committee usually does not approve hyphenated names. Mr. Buehler suggested not capitalizing the letter D in the name, but was not sure that the committee would approve that change.

Dr. Lipicky suggested changing the name. The firm asked about the tablet imprinting; if the name were changed, the dyes would have to be changed. They were informed that they may have to do comparative dissolution between the tablets and were referred to the SUPAC IR guidance.

Medco said that they would like to retain the name. They may appeal the decision by the Labeling and Nomenclature Committee to Dr. Lipicky or Temple.

Advisory Committee

Dr. Lipicky informed Medco that we would be taking the BiDil application to the February Advisory Committee meeting. He said that they should schedule a meeting to discuss preparing for the committee meeting. Usually, he said that we plan to send any written material to the Advisory Committee members at least 1 month before the meeting.

The firm questioned why the application was being taken to the Advisory Committee. They said that it had already gone years ago. Dr. Lipicky said that all the committee members have changed. Also, when the V-HeFt Trial was originally discussed, there was not a pending application, and it was before the V-HeFt II trial was done.

He said that the issues relating to the application could be discussed at the upcoming meeting.

Missing Data

Dr. Ganley said that the majority of patients in V-HeFT I do not have a last clinic visit recorded on or after December 15, 1985. He said that he could not document what happened to these patients between their last clinic visit and the end of the trial on 12/15/85. Dr. Cohn said that all patients were called on 12/15/85 or after to confirm the trial endpoints. He said that the documentation from these telephone calls may not have been submitted.

Dr. Ganley said that he needed these data to confirm the final mortality and hospitalization numbers for the trial. Only 9 patients have a clinic visit documented on or after 12/15/85. Medco said that they would obtain the documentation of the telephone calls confirming the patient status on 12/15/85.

ACTION ITEMS

Medco said that they will submit the revised protocol for the multiple-dose kinetic study and their response regarding their tradename as soon as possible.

Medco said that they would obtain the missing data regarding the last clinic visit (or call) for the patients in V-HeFT I and submit them to the NDA.

Dr. Parry will contact Mr. Buehler to arrange a meeting to discuss the upcoming Advisory Committee meeting.

Minutes Taken by: Gary Buehler 11/8/96

Gary Buehler

Concurrence, Chair Ray Lipicky 11/13/96

Raymond Lipicky, M.D.

Orig NDA
HFD-110
HFD-110 GBuehler
HFD-110 SBenton
HFD-860 PMarroum
RD: CGanley 11/8/96, PMarroum 11/8/96

Buehler

SEP 16 1996

MINUTES OF AN INTERNAL TELEPHONE CONFERENCE

Date: September 12, 1996

Subj: NDA 20-727 BiDil (hydralazine HCl and isosorbide dinitrate) Tablets
Medco Research

Meeting Chair: Raymond Lipicky, M.D.

Recorder: Gary Buehler

Participating:

Raymond Lipicky, M.D.	Director, Div. of Cardio-Renal Drug Products, HFD-110
Charles Ganley, M.D.	Supervisory Medical Officer, HFD-110
Patrick Marroum, Ph.D.	Team Leader, Div. of Pharm. Evaluation I, HFD-860
Gary Buehler	Reg. Health Proj. Manager, HFD-111

BACKGROUND/OBJECTIVES

On September 10, 1996, a telephone conference was held with Medco Research and their pharmacokinetic consultants [ ] to discuss the protocol for their multiple-dose pharmacokinetic study for BiDil (see minutes appended). At the conclusion of that discussion, we informed the firm that we would have to consult with Dr. Lipicky on the following issues:

1. Does the study have to be done with the highest dose?

2. Does the study have to be done in CHF patients?

3. What impact will the fact that the BiDil formulation that the firm plans to market is not bioequivalent to the formulations that were used in the V-HeFT I and I trials?

DISCUSSION POINTS

The issues were presented to Dr. Lipicky by Drs. Ganley and Marroum. It was emphasized that this formulation had never been given to any CHF patients, and that we have no pharmacokinetic data on the formulation except for the single-dose bioequivalence trial that was submitted with the NDA. We do not know how the formulation will behave after multiple dosing.

The bioavailability of the BiDil formulation (specifically the hydralazine portion of the formulation) was also discussed. It falls between the bioavailabilities of the two formulations used in the V-HeFT I and II trials, being more bioavailable that the tablet formulation used in the V-HeFT II trial but less bioavailable than the capsule formulation used in the V-Heft I trial. Of the two, it more closely resembles the formulation used in the V-HeFT I Trial.

DECISION

Dr. Lipicky said that we should have descriptive kinetics on the formulation, and ideally it should be in CHF patients and include the entire dosing range. He said that he understood the

firm's reluctance to do a multiple dose study in volunteers at the highest dose. He could not, however, see why there would be a problem in CHF patients since they are the patients expected to take the drug. He suggested that they do the trial in CHF patients. They should start dosing with the lowest dose. When steady state is reached, they should ramp up to the next highest dose and give it until steady state is reached. They should do this until the entire range is covered. Dr. Marroum said that steady state is reached after 5 doses. Dr. Lipicky said that all patients may not be able to tolerate the highest doses. If so, they will drop out at the highest dose tolerated. This study will enable us to collect descriptive pharmacokinetics at each dose at steady state and also assess the tolerability of the formulation in CHF patients.

ACTION ITEMS

Mr. Buehler will inform the firm of the decision. Dr. Lipicky agreed to meet with the firm if they wish.

/s/

Recorder: Gary Buehler 9/16/96

Gary Buehler

/s/

Concurrence, Chair Ray Lipicky 9/17/96

Raymond Lipicky, M.D.

Attachments: Minutes from 9/10/96 Telephone Conference with Medco

Orig NDA
HFD-110
HFD-110 GBuehler
HFD-110 SBenton
RD: PMarroum 9/16/96
CGanley 9/16/96

G. Buehler

SEP 16 1996

MINUTES OF A TELEPHONE CONFERENCE

Date: September 10, 1996

Subj: NDA 20-727 BiDil (hydralazine HCl /isosorbide dinitrate) Tablets
Discussion of Multiple-Dose Pharmacokinetic Study

Sponsor: Medco Research
Research Triangle Park, NC

Meeting Chair: Charles Ganley, M.D.
Sponsor Lead: Anne McKay
Recorder: Gary Buehler

Participating:

FDA

Charles Ganley, M.D.	Supervisory Medical Officer, Div. of Cardio-Renal Drug Products, HFD-110
Patrick Marroum, Ph.D.	Team Leader, Division of Pharmaceutical Evaluation I, HFD-860
Gary Buehler	Reg. Health Proj. Manager, HFD-111

Medco

Anne McKay	Regulatory Affairs
Cesare Orlandi, M.D.	Head, Research and Development

[ ] (Consultants)

Meeting Requested: 9/6/96

BACKGROUND

Medco submitted the NDA for BiDil on July 3, 1996. Before submission of their NDA, the firm had meetings with Division personnel to determine what would be required for the application. At a meeting held with the Biopharmaceutics reviewers, they were informed that a multiple-dose study would be required to describe the pharmacokinetic characteristics of their formulation due to the fact that the bio study that they performed to link the clinical formulation with the to-be-marketed BiDil formulation was done using a single-dose design. Because of the non-linear nature of the pharmacokinetics of hydralazine and ISDN, however, it is difficult to extrapolate the results of the study to a multiple-dose setting. They were, therefore, contacted by Dr. Marroum and informed that they would also have to do a multiple-dose trial to describe the characteristics of their formulation (this was done after consultation with Dr. Lipicky). They were also informed, however, that the study would not have to be submitted with their NDA, but the results would have to be submitted before any approval action. The firm submitted the protocol for the trial on August 9, 1996. Dr. Marroum completed his review of the protocol on August 21, 1996 (appended to the minutes). Comments

from the review were forwarded to the firm, and they requested the telephone conference to discuss the comments.

MEETING OBJECTIVES

The objective of the meeting was to reach agreement as to what would be an acceptable protocol for the multiple-dose pharmacokinetic trial for the BiDil NDA.

DISCUSSION POINTS

Scientific Rationale for the Study

Medco asked Dr. Marroum to discuss the scientific rationale for requiring the multiple-dose study. Dr. Marroum stated that it is a regulatory requirement to describe the pharmacokinetics of a formulation. In addition, we do not know what type of plasma levels to expect when this formulation is given in a multiple-dose regimen due to the non-linear nature of the pharmacokinetics of both hydralazine and ISDN.

Dr. [redacted] said that the information was clinically irrelevant since the drugs are not dosed on the basis of plasma levels. Dr. Marroum said that very few drugs are dosed on the basis of plasma levels, but we still require that the pharmacokinetic characteristics of the formulation be described. Knowing the highest plasma levels after chronic administration provides an added level of comfort, especially since this formulation was never administered to CHF patients (the target population for which the drug is indicated).

Dose

The consultants said that the trial cannot be done with volunteers using the highest dose. Eleven of the 12 volunteers who participated in the single dose trial would not come back after receiving the first dose. The problems experienced were hypotension and headache. The Agency suggested using CHF patients, but because of the phenotyping, screening for drug and assay interactions and inability to tolerate the high dose in this population (50% of the V-HeFT patients could not tolerate the highest dose), they believe that they would have to screen 80 patients to get the 12 needed for the study.

The firm proposed doing the study in volunteers at the lower dose. Dr. Ganley thought that, despite the problems detailed above, it could be done in CHF patients at the highest dose.

Non-bioequivalence of formulation

The study comparing the firm's new formulation with the formulation used in the V-HeFT trials was briefly discussed. Dr. Marroum said that the formulation being proposed for marketing was not bioequivalent to the formulation used in the V-HeFT trials, and in fact it was up to 40% more available. Dr. Ganley said that, in light of this difference, he was uncomfortable considering approval for a formulation that had never been given to CHF patients. He thought that this was more reason to ask that the pharmacokinetic study be done in CHF patients.

DECISIONS

The firm was informed that Dr. Lipicky would have to be consulted regarding the multiple-dose pharmacokinetic study and the non-bioequivalence question.

ACTION ITEMS

Mr. Buehler will get back to the firm with our decision after consulting with Dr. Lipicky.

Minutes prepared by: Gary Buehler 9/16/96

Gary Buehler

Concurrence, Chair

Charles Ganley, M.D.

Orig NDA
~~HFD-110~~
HFD-110 GBuehler
HFD-110 SBenton
RD: PMarroum 9/12/96
CGanley 9/16/96

3 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(5) Deliberative Process

____ § 552(b)(4) Draft Labeling

9-10-96

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-727

SEP 10 1996

Medco Research, Inc.
Attention: Ms. Anne McKay
85 T.W. Alexander Drive
Research Triangle Park, NC 27709

Dear Ms. McKay:

Please refer to your pending July 3, 1996 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for BiDil (hydralazine hydrochloride/isosorbide dinitrate) 75/40, 75/20, 37.5/20, and 37.5/10 mg Tablets.

We have completed our review of the manufacturing and controls section of your submission and have identified the following deficiencies:

1. Please determine the residual solvents impurities amounts [ ] in the hydralazine hydrochloride drug substance lots 408015, 409024, 410020 and also in any other lots that you have used in manufacturing commercial batches of BiDil drug product. Also delete the USP [ ] from the specifications and test methods for the hydralazine drug substance. These solvents are not used in the syntheses.

2. Please correct your specification for [ ] This is the specification set by the DMF holder [ ] Also include [ ] specification of NMT [ ] in your specification for the diluted drug substance.

3. Please provide the stability data on the diluted ISDN drug substance [ ] used for the drug product. A letter in this regard is also being written to [ ]

4. Please provide the in-process control methods for determination of hardness and thickness of the film coating process and set specifications for these in-process controls used in the manufacturing of the drug product.

5. Please provide rework procedure for the drug product if you plan to rework any production batches.

6. Please describe the packaging operations, including type of equipment and operative conditions.

7. Please provide stability data on each of 3 production lots of drug product that are at least [ ] of the commercial batch or [ ] units whichever is larger as the data become available. Also provide the batch record for lot DG-35.

8. The Agency reserves comment on the proposed expiration date until additional stability data are received.

9. Your dissolution data for [ ] for batches CW74 and CW 75 show a large variation in the individual results. To evaluate the dissolution specification, it is necessary for you to submit additional dissolution data (individual results) at the [ ] time interval on the newer batches. We may have additional comments after the Biopharmaceutics review is completed.

10. Please submit any pharmacological and/or toxicological data you may have developed for the BiDil drug product. We suggest you evaluate the interaction between the two new drug substances and possible toxicity of any reaction product. Please refer to our letter of July 1993 in response to your IND 41,816.

11. Please list the excipients in alphabetical order in the **DESCRIPTION** section of the package insert and also include the ingredients in Opadry, the coloring agents that are used in the film coating of drug product.

12. Please indicate on the container labels that the tablets are manufactured in [ ]

13. Please provide three separate copies of methods validation documents.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact:

Mr. Gary Buehler
Regulatory Health Project Manager
(301) 594-5332

Sincerely yours,

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

cc:
Original NDA
HFD-110
HFD-110/Project Manager
HFD-110/KBongiovanni
sb/8/19/96;8/27/96
R/D: GBuehler/8/20/96
JAdvani/8/26/96
RWolters/8/26/96
NMorgenstern/8/27/96

INFORMATION REQUEST

FAX Transmittal

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products

Transmitted to FAX number: 919-549-7515

Attention: Anne McKay

Company name: Medco Research

Phone:

Subject: BiDil Protocol

Date: 8/21/96

Pages including this sheet: 2

From: Gary J. Buehler
Phone: (301) 594-5332
FAX: (301) 594-5494

Gary
Signature

cc: IND/NDA _____
HFD-110
HFD-111/CSO

BACKGROUND:

Bidil[R] is a fixed combination formulation consisting of 2 active ingredients, hydralazine HCl and isosorbide dinitrate (ISDN) which is being developed for the treatment of congestive heart failure. Hydralazine is an antihypertensive agent that lowers blood pressure by exerting a peripheral vasodilating effect on the arterial vascular bed. ISDN is a vasodilator which has effects primarily on the venous system. The effects of the coadministration of both these drugs were studied in 2 large multi center clinical trials.
On July 3rd 1996, a New Drug Application was submitted for Bidil for the treatment of congestive heart failure in patients intolerant to ACE inhibitors. As discussed in several telephone calls and as committed to within the NDA, the sponsor is submitting a draft protocol for the agreed upon multiple dose pharmacokinetic study.
A summary of the proposed protocol is submitted as Appendix I.

COMMENTS:

1-The sponsor intends to use the lowest strength tablets for this multiple dose study. Since these two drugs exhibit non linear characteristics in their absorption, it is recommended that the sponsor uses the highest strength tablets (the 75/40 mg). The study with the highest strength would give an idea on the highest plasma concentrations that are achieved with Bidil following chronic administration. Moreover, the results that might be obtained from the lowest strength tablets might not be extrapolatable to the higher strength due to the nonlinearities that might be caused by saturation of the first pass effects

2-Giving the highest dose of Bidil to normal volunteers might result in excessive hypotension and headache which would lead a lot of subjects to drop out. One way to avoid this problem is to start with the lowest strength and slowly escalate the dose of Bidil until the highest strength is reached. This would allow the subjects to build tolerance to the side effects and thus would minimize the probability of dropping out. If the sponsor opts to, sparse blood samples could be collected to obtain an idea on the plasma levels achieved.

45 DAY FILING SUMMARY

Date: August 2, 1996

NDA 20-727 BiDil (hydralazine HCl and isosorbide dinitrate) Tablets

Sponsor: Medco Research, Inc.
PO Box 13886
Research Triangle Park, NC 27709

Date of Submission: July 3, 1996

Date of Receipt: July 3, 1996

User Fee Date: July 3, 1997

BACKGROUND

This application uses the V-HeFT I and V-HeFT II trials as pivotal studies as support for the indication of treatment of congestive heart failure as an adjunct to standard therapy (dig. and diuretics) in patients who are intolerant or have a contraindication to ACE inhibitors. They claim that the therapy improves survival and exercise tolerance.

A pre-IND meeting was held for this combination product on November 5, 1992. During that meeting, Dr. Lipicky discussed the issues that would have to be addressed in an NDA submission for the product. The minutes of that meeting are appended to this document.

REVIEW TEAM

Medical - Dr. Ganley Secondary - Dr. Lipicky

Dr. Ganley will not be able to start his review until the fall.

Statistical - Dr. Hung

Biopharm. - Dr. Marroum

The firm has not yet completed their multiple-dose pharmacokinetic trial (a single-dose trial was submitted with the NDA). They were informed that they could submit their NDA without this trial, but they would have to have it completed and reviewed by us before possible decision. The protocol has not yet been submitted for this trial.

Pharmacology - Dr. Belair

No original animal studies were done for this application. The firm has done a literature/FOI review of available data on hydralazine and ISDN and submitted it to the NDA.

Chemistry - Dr. Advani

EIR - Submitted 7/26/96

Environmental Assessment - Dr. Zielinski

The EA has been submitted and initially reviewed by Dr. Zielinski.

DSI - Dr. El Hage

Dr. Lipicky decided that clinical trial inspections will not be required for the V-HeFT I and II trials.

Regulatory Requirements/Organization - Mr. Buehler

The application appears to be well organized and indexed. Patent information and debarment certificate were included. Because of the referencing of the Pharmacology/Toxicology data, the application should be considered a 505 (b)(2) submission. The firm was called and asked to submit the proper patent certification for this type of submission. The firm replied that, because they had done a literature/FOI search of the available animal data for the two compounds, they thought that it would be considered a 505 (b)(1) application. I informed them that since the actual data have not been submitted, it is considered a (b)(2).

They have submitted a full user fee for the application. I checked with Mr. Hassall to determine whether this 505 (b)(2) application would require a fee. He said that since it is for a new indication for the combination product, containing full clinical studies, it would require a full fee.

Gary Buehler 8/2/96

Gary Buehler, Project Manager

Orig NDA
HFD-110
HFD-110 GBuehler
HFD-110 SBenton

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-727

Medco Research, Inc.
Attention: Ms. Anne McKay
85 T.W. Alexander Drive
Research Triangle Park, NC 27709

JUL 15 1996

Dear Ms. McKay:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: BiDil (hydralazine hydrochloride and isosorbide dinitrate) Tablets

Therapeutic Classification: 4S

Date of Application: July 3, 1996

Date of Receipt: July 3, 1996

Our Reference Number: NDA 20-727

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on September 1, 1996 in accordance with 21 CFR 314.101(a).

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

Natalia A. Morgenstern
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc
Orig. NDA
HFD-110
HFD-110/Project Manager
DISTRICT OFFICE
HFD-110/PAlexis/7/8/96
sb/7/11/96
R/D: GBuehler

ACKNOWLEDGEMENT - AC

BUEHLER

MINUTES OF A 45 DAY FILING MEETING AUG 23 1996

Date: August 2, 1996

Subj: NDA 20-727 BiDil (hydralazine HCl and isosorbide dinitrate) Tablets

Medco Research, Inc.
PO Box 13886
Research Triangle Park, NC 27709

Date of Submission: July 3, 1996

Date of Receipt: July 3, 1996

User Fee Due Date: July 3, 1997

Meeting Chair: Raymond Lipicky, M.D.

Recorder: Gary Buehler

BACKGROUND

See 45 day filing summary and minutes of the Pre-IND Meeting held on November 5, 1992.

REVIEW TEAM

Medical - Dr. Ganley
Statistical - Dr. Hung

Drs. Ganley and Hung will do a combined medical/Statistical review for the application. They will not be able to start the review until October 1996. Their projected completion date would be February 1997. The secondary medical review will add another month.

Pharmacology - Dr. Belair

No original animal studies were submitted with the application. The firm has done a literature/FOI review of available data on hydralazine and isosorbide dinitrate. Dr. Lipicky said that we must look at what was submitted, but little in the way of a review was needed. Dr. Belair said that he could complete his assignment by the end of August.

Biopharmaceutics Dr. Marroum

The firm has not yet completed their multiple-dose pharmacokinetic study, and in fact we are still waiting for them to submit the protocol for review. They were informed that this study would not have to be submitted with the NDA, but that the NDA could not be approved absent these data. Dr. Marroum said that they have only submitted one single-dose study with the NDA. He said that he will be finished his review by the end of September.

Chemistry - Dr. Advani

Dr. Advani has started his review. He said that they need 12 month stability on 3 batches of drug product, and they only have submitted [ ] data on 2 batches. They have said that they plan to produce another batch in May, but they may not be able to have the 12 month stability completed on this batch by July 1997. In addition, they were requested by Dr. Weiss to do a chemical interaction study to determine that the two components of the product do not interact with each other to form possible nitroso compounds. They have not done this, nor do they plan to.

Dr. Lipicky said that the firm should be instructed to look for possible nitroso compound formation.

Dr. Advani said that he will complete his review before the end of August.

Environmental Assessment - Dr. Zielinski

The environmental assessment review will be completed before the end of September.

DSI - Dr. El Hage

Dr. Lipicky has determined that an audit of the V-HeFT I or II trials is not necessary.

Advisory Committee

It seems that this application would be a likely candidate for an advisory Committee meeting. It will probably go in January or May 1997 depending on the progress of the reviews.

Summary

The application was administratively well organized and indexed. Patent information and debarment certificate were included. An appropriate patent certification for a 505(b)(2) application (citing no applicable patents) will be submitted.

The application appeared acceptable for filing. Projected time to first decision will be March 1997.

Recorder Gary Buehler 8/15/96

Gary Buehler

Concurrence, Chair Ray Lipicky 8/22/96

Raymond Lipicky, M.D.

Orig NDA
HFD-110
HFD-110 GBuehler
HFD-110 SBenton

GB

JAN 16 1996

MINUTES OF A TELEPHONE CONFERENCE BETWEEN FDA AND MEDCO RESEARCH

IND 41,816 BiDil (hydralazine HCl and isosorbide dinitrate) Tablets

Pre-NDA Meeting Computer Discussion

Date: November 30, 1995

Participating:

Medco

Jan Parry	Regulatory Affairs
Ann McKay	Regulatory Affairs
Victor Molina	Clinical Research
Gordon Davis	Statistician
Donna Rogers	System Information

FDA

N. Stockbridge, M.D., Ph.D.	Medical Officer, Division of Cardio-Renal Drug Products, HFD-110
Maryann Gordon, M.D.	Medical Reviewer, HFD-110
Ameeta Parekh, Ph.D.	Team Leader, Div. of Pharmaceutical Evaluation I
Patrick Marroum, Ph.D.	Team Leader, Div. of Pharmaceutical Evaluation I
James Hung, Ph.D.	Biometrics Reviewer, Div. Of Biometrics, HFD-713
Gary Buehler	RHPM, HFD-110

BIOPHARM ISSUES

The meeting was scheduled to discuss the upcoming NDA submission for BiDil (hydralazine HCl and isosorbide dinitrate) Tablets and specifically what computer formats will be used for the respective sections of the submission. Before the computer discussion began, however, Dr. Marroum wanted to discuss an issue relating to the bioequivalence study that is being done by the firm.

Dr. Marroum said that the study linking the clinical trial formulation with the to-be-marketed formulation is being done as single-dose rather than multiple-dose as recommended by the Division. He said that we need a multiple-dose study in order to provide descriptive pharmacokinetics for the formulation. Dr. Molina stated that they have provided a rationale as to why the study was done as single rather than multiple-dose. Dr. Marroum stated that their rationale was acceptable for bioequivalence purposes; the BE study did not have to be multiple-dose. We must, however, have some study done as multiple-dose to define the pharmacokinetics of the formulation. Since this is the only PK study that will be performed, it was recommended that it be multiple-dose to address this need.

Dr. Molina said that they did not believe that they could expose volunteers to multiple doses for BiDil. Dr. Marroum said that they could do the study in patients. Dr. Molina asked what information the study would provide. Dr. Marroum said that it would provide information about blood levels at steady state with the final formulation. At this time, only single doses of the final formulation fixed-ratio tablets have been given, and the multiple-dose kinetics of this final

formulation are unknown. The V-HeFT trial used capsules and tablets of hydralazine HCl plus tablets of Isordil given simultaneously.

Dr. Molina said that their data base consists of a mortality trial. Why would they be worried about blood levels? Dr. Marroum said that it did not have to be a large study, and it may be done in volunteers or patients - their choice. Dr. Molina stated again that the mortality effect of the V-HeFT trial should address any concerns. Dr. Marroum said that the there may be an effect when the drugs are combined into one formulation. We do not think so, but we would like to know.

Since the only blood level data we have are from the single-dose relative bioavailability study, we do not have any knowledge whether ISDN or hydralazine are going to affect each other upon chronic dosing, especially since the sponsor is claiming that tolerance to QID dosing of ISDN is not a problem. Also the mechanism for this lack of tolerance is not known and may have a problematic basis. Thus by performing a multiple-dose PK study on BiDil, the firm will be able to show that single dose PK is predictive or not, give an idea of the blood levels achieved and also be able to show whether the steady-state pharmacokinetics of this combination are comparable to the steady-state PK of the 2 drugs dosed individually. This would rule out any effect that the two drugs may have on each other.

Dr. Parekh asked if fast and slow acetylators were included in the clinical trials. The firm stated that they did not know. Dr. Parekh said that the subjects entered into the multi-dose trial should include fast and slow acetylators; a further benefit of the trial will be the data provided on these patients.

The firm asked about the number of doses that should be included in the trial. Dr. Marroum said that they must give enough doses to get to steady state.

Dr. Marroum stated that this issue was discussed with Dr. Lipicky. He stated that the data should be provided, but it will not hold up the filing of the NDA if it cannot be provided at that time. It must, however, be provided before approval.

Addressing another issue, Dr. Parekh stated that a food effect study will not be required for this application, but if not provided, the package insert will state that the effect of food is unknown. In the absence of a food effect study, the sponsor should attempt to characterize the effect of food on both hydralazine and ISDN by reviewing the current literature.

COMPUTER ISSUES

The firm provided a listing of agreements made with regard to the computer filing of the application. This list is appended to the minutes.

Gary Buehler
/S/ 1/16/96

Orig IND
HFD-110
HFD-110 GBuehler
HFD-110 SBenton
RD: NStockbridge 12/12/95, MGordon, 12/12/95, AParekh 12/12/95
PMarroum 12/12/95, JHung 12/12/95

COMPUTER ISSUES

Dr. Stockbridge reviewed the list of issues faxed by Medco for the meeting(attached). He also advised that all of the reviewers in the Cardio-Renal Division (with one exception) use Macintosh computers and Word Perfect word processing.

Following along from the issues list, the agreements are as follows:

I. Pivotal Study Datasets - V-HeFT I and II

It was agreed that SAS® datasets delivered to the agency on diskettes in SAS Transport format is acceptable. We are required to submit the validation data confirming the summary data in the ANALYSIS dataset is correct relative to the CRF form-specific records in the MAIN dataset. Dr. Hung requested that all analysis software be provided, including the Monte Carlo simulation programs used by Dr. Lloyd Fisher with the exception of the BMDP longitudinal data analysis.

Dr. Gordon wishes to receive the Case Report Forms on disc. CD ROM is acceptable. We explained that this was a big exercise especially with regard to the indexing required. Medco agreed to investigate the matter further and provide feedback to the FDA with regard to the feasibility of providing this data.

II. Bioavailability Datasets - CB-01 and CB-02

Submission of ASCII files in Lotus® or SAS transport format is acceptable. FIS is not required nor used anymore.

It was noted that the Division of Biopharmaceutics uses IBM computers and Word Perfect word processing.

III. NDA Documents

Dr. Gordon requested the protocols and all amendments for the V-HeFT I and II protocols be provided on disc. As discussed, the amendments will be in the form of minutes of the Data Monitoring Board.

With regard to other documents, FDA advised that submitting these in Microsoft Word is acceptable and that most word processing programs were compatible with the Macintoshes. We agreed to investigate an online index system for locating all documents in the NDA. We also agreed to submit the labeling in a machine readable automatic line numbering system.

BiDil NDA Data Transfer Issues

I. Pivotal Study Datasets (V-HeFT I & II: total n=1263)

- Analysis dataset in SAS has one observation per patient with summary variables such as survival days. The efficacy analysis is generated from this dataset.
- Main dataset contains all data collected in CRF for each visit. Examples: every Adverse Event and every treatment prescription. This is required for ISS analyses.
- *Identify optimal SAS dataset transfer procedure, including version and media.*
- *Discuss cost/benefit issues relating to scanning CRF pages onto optical disc.*

II. Bioavailability Study Datasets (CB-01 & 02: total n=161)

- CRF patient visit data managed and analyzed with SAS.
- Pharmacokinetic parameters calculated from plasma concentration data using Lotus. Data transferred to SAS for generation of descriptive statistics and listings.
- *Identify optimal SAS dataset transfer procedure, including version and media.*
- *Determine if FIS datasets are desired for biopharmaceutical data.*

III. NDA Documents

- All reports were generated with Microsoft Word.
- *Identify word processing software desired for report text files.*
- *Determine if a document navigator software system would be beneficial.*

MINUTES OF A MEETING BETWEEN
FDA AND MEDCO RESEARCH

NOV 20 1992

Date: November 5, 1992

Subj: Pre-IND Meeting Bidil (hydralazine HCl and isosorbide dinitrate) Oral
V-HeFT Trials

Attending:

Medco

Jay Cohn, M.D.	Prof. of Medicine, U. of Minn., Consultant
Sam Teichman, M.D.	Medical Director, Medco Research
Lloyd Fisher, Ph.D.	Statistical Consultant,
M. Holbrook, BA	Dir., Data Management and Biostatistics
B. Johnson, MA	Regulatory Specialist

FDA

Robert Temple, M.D.	Director, ODE I, HFD-100
Raymond Lipicky, M.D.	Dir., Div. of Cardio-Renal Drug Products, HFD-110
Milton Packer, M.D.	Consultant to FDA
Nicholas Fleisher, Ph.D.	Dir., Pharmacokinetics Eval Branch, HFD-426
George Chi, Ph.D.	Supervisory Statistician, HFD-713
James Hung, Ph.D.	Statistical Reviewer, HFD-713
Ursula Hoppe, M.D.	Visiting Scientist, BGA
Gary Buehler	CSO, HFD-111

BACKGROUND

Medco asked to meet to discuss the viability of submitting an NDA for a fixed combination product of hydralazine hydrochloride and isosorbide dinitrate using the V-Heft I and II studies as clinical support.

Dr. Lipicky opened the meeting by stating the issues regarding the submission of an NDA for the above combination.

BIOAVAILABILITY: He stated that the bioavailability issue must be addressed. There must be some link provided between the formulation(s) used in the V-HeFT studies and the formulation that is intended for marketing.

STATISTICAL STATUS OF V-HEFT I: We have had numerous meetings to discuss the statistical significance of the V-HeFT I trial. Ordinarily we would insist that the pre-specified analysis would be the only one accepted. With this trial, however, we have discussed other options. This decision and the results of the modified analysis will have to be evaluated.

TOLERANCE: Isosorbide dinitrate has been shown to produce tolerance when given in a continuous fashion. This combination, however, indicates that this drug is to be given in just the dosage regimen that we are saying should be avoided. This issue must be addressed and explained because the labeling of this product would be counter to the approved ISDN labeling.

RELATIONSHIP TO ACE INHIBITORS: In evaluating the databases of the V-HeFT I and II trials, it was decided that the only indication that could be awarded to this combination would be preservation of mortality in patients that cannot take ACE inhibitors. This indication would depend on the results of the statistical re-analysis of the V-HeFT I trial to be positive. In response to a statement by Dr. Teichman, Dr. Lipicky stated that there is absolutely nothing to support the use of this combination instead of ACE inhibitors. In a positive controlled trial against enalapril, the combination lost and we could not consider giving an indication that would make it an alternative to a therapy that had been shown to be superior in preserving mortality.

PRESENTATION OF DATA

The data from the V-HeFT I and II trials were presented by Drs. Cohn, Teichman and Fisher. Briefly the V-Heft I trial showed an increase in mortality for the hydralazine/isosorbide group with a pre-specified p of .09. After adjustment for covariates according to a statistical model, the p value remains to be determined. The trial did not demonstrate any effect on symptoms of CHF. V-HeFT II was a positive-controlled mortality trial done against enalapril. The hydralazine isosorbide combination was inferior to enalapril in preserving mortality but was superior to enalapril for peak oxygen consumption. There were no differences in symptoms of CHF, quality of life and number of hospitalizations between the two groups. Summarizing from the two trials, we have a mortality effect form the first trial (that is yet to be determined whether the p value is adequate) and an efficacy effect (according one parameter) in the second trial.

The following issues were addressed during their presentation:

1. Quality of Life - Dr. Teichman stated Hyd/Iso improved the quality of life of the patients because it improved exercise tolerance (from the peak oxygen consumption measurements) and increased left ventricular ejection fraction. Dr. Packer requested evidence that supported this contention. No one in the room (including the consultants to Medco) supported this statement.

2. Exercise Duration Measurements - Dr. Packer asked Dr. Cohn about the exercise duration measurements for V-HeFT II. Dr. Cohn stated that they were not reported because they were not a primary endpoint. He said that they parallel the peak oxygen consumption (VO_2) measurements.

3. Superimposition of Mortality Curves - During his presentation, Dr. Cohn superimposed the mortality curves from the V-HeFT II trial (hyd/iso and enalapril) on to the curves from V-HeFT I (hyd/iso and placebo). He was impressed that the curves for the hyd/iso arms on each study were almost superimposable. Dr. Packer did not think that to be a logical comparison. He stated that the studies were done at different times, in a different patient population with different baseline characteristics and using different doses. Also, by doing this it could be inferred that hyd/iso would have been better than placebo in both trials. Using this rationale,

however, would lead one to believe that the enalapril group had a 50% reduction in mortality when compared to the placebo group in V-HeFT I. We know the mortality effect of enalapril is about 17% from other studies, making the comparison across studies to be totally invalid. Dr. Packer stated that he thought that it was just a coincidence that the curves superimposed. Dr. Fisher agreed with Dr. Packer.

4. Mortality Claim - Dr. Cohn stated that enalapril clearly was superior to hyd/iso in V-HeFT II. He did not want to suggest therefore that hyd/iso be used in place of enalapril for mortality. He stated, however, that 70% of CHF patients are not getting ACE inhibitors. Reasons cited are cost and renal failure associated with ACE inhibitors. He maintained that hyd/iso would be an acceptable alternative for these patients.

At the conclusion of the data presentation, Dr. Lipicky addressed the following major issues that would impact upon the filing and review of this application:

PHARMACOKINETICS

Dr. Lipicky stated that, assuming that V-HeFT I and II are accepted as pivotal trials, the dosing promulgated in these trials would have to be equivalent to the form of the combination of the drugs that the firm wants to market. He stated that because the kinetics of both drugs are not linear, the studies done must be multiple dose. He also recommended that, to protect against variability that would lead one to assume an unacceptable formulation, a solution are should be incorporated. He stated that, overall, the goal would be to show that the to-be-marketed formulation is clinically close enough to the formulation used in the clinical trials to be considered equivalent. He stated that the more that the two formulations are different, the more problems there would be.

Dr. [ ] stated that two different formulations were used in the two trials. He asked if they could just study the formulation that was used in V-HeFT II. Dr. Lipicky stated that he could not answer that question at this time. He further stated that the more that the formulation(s) are different, the greater chance of losing.

Dr. Fleisher spoke with the firm privately after the meeting. His comments are contained in a memo appended to these minutes.

STATISTICAL STATUS OF V-HeFT I

Dr. Fisher stated that he has not done the analysis of V-HeFT I using the adjusting factors that were suggested by Dr. Packer. He stated that Dr. Johnson at the VA has done them and it is his understanding that they are all significant. He could not address the goodness of fit. Dr. Hung stated that all values must be included.

Dr. Lipicky stated that it remains to be seen whether we will accept this last analysis. He said that we usually hold the sponsors to one analysis and do not allow playing with the data.

CLINICAL SUPPORT

Dr. Packer addressed the adequacy of the database. For discussion purposes, he stated that the statistical analysis for V-HeFT I was acceptable and that we accept that the drug has a mortality effect. Since FDA policy is to accept one trial for a mortality claim, the firm would have a claim for patients that cannot take ACE inhibitors. Regarding symptoms of CHF, however, the standard is two adequate and well-controlled trials. The only support for a CHF symptom claim would be V-HeFT II. The issue of tolerance with nitrates has also not been addressed. Dr. Cohn explained that the addition of hydralazine to the nitrate protected against tolerance. He stated that he has animal studies to support this. Dr. Lipicky stated that we must have support in humans. A hemodynamic drug interaction study was recommended.

Dr. Packer summarized by stating that an exercise tolerance trial done in patients who are taking ACE inhibitors, using the to be marketed form of the drug, seems to be indicated. Hemodynamic measurements could be taken in this trial to support the protection from tolerance claim. This would address the issues of tolerance, a second efficacy trial, and provide a trial in patients using the marketed form of the drug. Absent this trial, the database could possibly support a mortality claim in patients who are not able to take ACE inhibitors.

Gary Buehler 11/20/92
Gary Buehler, CSO

Orig IND (when filed)
HFD-110 file
HFD-110 SBenton
HFD-110 GBuehler

FEB 12 1991

Minutes of a Meeting
Between
FDA
And
Dr. Jay Cohn and Wyeth-Ayerst

Date: January 11, 1991

Subject: Statistical Analysis of V-HeFT trial
NDA 12-093 Isordil (isosorbide dinitrate) Tablets

Attending: Wyeth-Ayerst et al
Ray Baranello, Wyeth-Ayerst
Philip deVane, Wyeth-Ayerst
Harold Marder, Wyeth-Ayerst
Jay N. Cohn, M.D., University of Minnesota, VA Cooperative Program
Gary Johnson, Statistician, VA Cooperative Program
Lloyd Fisher, Consultant Statistician, Wyeth-Ayerst

FDA
Raymond Lipicky, M.D., Director, Division of Cardio-Renal Drug Products, HFD-110
Cheryl Graham, M.D., Deputy Director, HFD-110
Robert Fenichel, Ph.D., M.D., Supervisory Medical Officer, HFD-110
Milton Packer, M.D., Consultant to FDA
George Chi, Ph.D., Supervisory Statistician, HFD-713
James Hung, Ph.D., Mathematical Statistician, HFD-713
Gary Buehler, Consumer Safety Officer, HFD-111

The meeting was held to discuss the statistical analysis of the V-HeFT trial that was presented to the Advisory Committee on March 4, 1988. At that time, the Advisory Committee decided that, if the V-HeFT trial survives statistical analysis, a statement discussing the trial and its results could be added to the Clinical Pharmacology section of the labeling for isosorbide dinitrate and hydralazine.

The Veterans Administration Cooperative Study on Vasodilator Therapy of Heart Failure (VHeFT) Trial was designed to determine whether vasodilator drugs could alter the survival of patients with chronic congestive heart failure (CHF) treated with digoxin and diuretics. One hundred and eighty-six patients were randomly assigned to the combination of hydralazine (up to 100 mg QID) and isosorbide dinitrate (up to 40 mg QID); 273 to placebo and 183 to prazosin. Numerical results favored the hydralazine/isosorbide combination with respect to mortality. The statistical analysis, however, required certain adjustments. The Advisory Committee wanted to have the study independently reviewed by FDA statisticians.

Dr. Hung, after waiting almost 1 year to obtain the necessary data from the VA, completed his review on February 21, 1990. He found numerous problems with the study and the analysis. For mortality during the entire study period, there was strong evidence indicating a lack of fit of the Cox models used by the V-HeFT research group. Ejection Fraction, O_2 consumption, cardiothoracic ratio and use of antiarrhythmics appeared to violate proportional hazard (PH) assumption, linearity assumption or both. The Cox survival estimates seemed too optimistic, particularly for the entire study, and were unreliable in the opinion of Dr. Hung. The only viable method was the logrank test. This reduction, however, was not statistically significant at

the 5% level (p=0.093) based on the logrank test. In addition, the advantage of hydralazine/isosorbide dinitrate disappeared for some reason after the first 2 years in patients who had never stopped the medication but was observed for those who had at some point discontinued the medication.

Dr. Cohn acknowledged that it had been a long wait since the Advisory Committee meeting. He briefly outlined the rationale for using the Hydralazine/Isosorbide combination. The concept for the trial began with the search for an oral regimen to replicate the effect of nitroprusside. The combination of Hydralazine and Isosorbide produced a comparable hemodynamic profile. Dr. Cohn outlined the results of the V-HeFT study with respect to mortality for the Hydralazine/Isosorbide group as follows:

% reduction in mortality	Interval	p value
38%	1 year	.031
29%	2 years	.057
23%	3 years	.041
7%	4 years	.387

He stated that the designated endpoint chosen prospectively was 2 years. If, however, he had chosen one year, there would be no argument about the results. He further stated that the Consensus trial was analyzed at 1 year and showed only a 31% reduction of mortality for enalapril.

Statistical Adjustment

Since the purpose of this meeting was to resolve the difference of opinion regarding the statistical analysis, a major portion of the meeting was devoted to deciding if the Agency would accept the statistical adjustment proposed by Dr. Cohn and Mr. Johnson.

Dr. Cohn stated that previous studies have identified ejection fraction, clinical assessment of exercise intolerance and arrhythmias as prognostic variables in patients with CHF. Consistent with these previous observations, the mortality rate in V-HeFT was inversely related to ejection fraction and VO_2 during exercise and directly related to the cardiothoracic ratio and a history of antiarrhythmic drug use. Therefore, in the assessment of annual mortality rate in the various subsets analyzed, the all mortality experience should be able to be adjusted for any prerandomization imbalance in these variables.

Dr. Fisher expanded on why adjustment should be allowed. He acknowledged that there were no initial plans in the protocol to allow adjustment; he considered this a serious mistake. He stated, however, that whenever there are strong prognostic indicators that vary, an adjusted value makes the most scientific sense. The better explained these external variants are, the more precise the study.

Dr. Hung questioned the model chosen and if it was good enough to believe the p value. He also asked about the results of each interim analysis performed. He and Dr. Chi stated that they must have these results for their review.

Design Problems

Dr. Cohn acknowledged that the study, as performed, did have some design problems and emphasized that little was known about many variables affecting heart failure at the time it was designed (1978-79). Originally it was supposed to contain single arms for isosorbide and hydralazine. They were also not aware, at the time the trial was designed, of prazosin tolerance. The VA monitoring committee substituted an alternate statistical method and their data monitoring committee did not keep perfect records. Dr. Cohn and Mr. Johnson stated that they would contact the original statistician working on the project and any other members of the monitoring committee to get the interim analysis data and to determine if there was a plan to stop the trial after the interim analyses.

Replication

Dr. Lipicky stated that, despite the presented data, he is still not convinced that the effect could be replicated. The data do not fit the model and they are not overwhelming, needing many adjustments to achieve statistical significance.

Dr. Cohn asked about the ejection fraction (EF) data that he presented. Didn't that data and the fact that a positive effect on mortality seems to coincide with improvement in EF convince Dr. Lipicky that the effect was real?

Dr. Lipicky answered not necessarily so. He was skeptical because he knows that when isosorbide is used in a chronic manner, tolerance develops. He, therefore, had difficulty in believing any chronic effect that was at least partially attributable to isosorbide. Dr. Packer, however, believed that the EF effect was from the hydralazine and therefore thought it could be replicated.

Drop-Out Rate

Dr. Packer mentioned the high drop-out rate in the Hydralazine/Isosorbide group (32% of patients dropped out on 1 or both drugs). Also, the patients that dropped out seemed to have a persistent treatment effect. Dr. Cohn stated that they are evaluating that effect presently.

Regulatory Standard

Dr. Packer addressed the Agency regulatory standard in answering Dr. Cohn's question regarding the acceptability of the one year data. He said that a p value of .05 is accepted by the Agency for statistical significance. The question to be addressed is if this effect can be put into the labeling as an effect recognized by FDA.

Dr. Lipicky continued that applications that are approved are those that meet the a priori requirements specified in the protocol. If you have to make adjustments or changes in the statistical methods, the results of the trial become less credible. In this particular trial, the statistical method proposed in the protocol was not the one actually used by those doing the trial. Therefore we are now faced with selecting a statistical method. Because the trial has been completed, everyone knows what method will yield the most favorable result. If, therefore, we are expected to pick a method of analysis, we will pick the least favorable.

Plan

Dr. Lipicky stated that in order to resolve this dilemma he would allow some statistical adjustment. Dr. Packer could pick up to 10 treatment variables that could be used in the statistical reanalysis. However, Dr. Lipicky asserted that even if the adjusted analysis results in a statistically significant reduction in mortality ($p<.05$), he would still require the study to be replicated for labeling approval. He cited the following factors that made him have doubts about the ability to reproduce the trial results:

1. No other efficacy parameter (ETT) showed any significant improvements.

2. A high incidence of drug intolerability (many drop-outs and dosage reductions).

3. Uncertainty as to whether the combination of drugs was necessary (maybe hydralazine alone would give the same effect).

4. Only one trial.

If, of course, after reanalysis, the p value is above .05, the trial will not be acceptable.

The effect of V-HeFT II was also addressed. V-HeFT II is a mortality trial employing Isosorbide/Hydralazine against enalapril. If Isosorbide/Hydralazine is shown to be superior to enalapril it would provide compelling evidence for approval. If Isosorbide/Hydralazine is equivalent to enalapril, it would be supportive but would not guarantee approval.

Gary Buehler 2/12/91

Gary Buehler
Consumer Safety Officer

cc
Orig.
HFD-110
HFD-713/JHung
HFD-713/GChi
~~HFD~~-110/GBuehler;1/24/91
sb/1/22/91;1/30/91;2/1/91;2/11/91
~~R/D:~~ CGraham/1/24/91
RFenichel/1/24/91

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: AUG 8 1990

FROM: Director, Office of Drug Evaluation I
Director, Office of Drug Evaluation II

SUBJECT: Drug Studies in Pediatric Patients

TO: ODE I and II Directors, Deputy Directors, and Supervisory SCSO's

The attached checklist, "Drug Studies in Pediatric Patients" (the "pediatric page"), has been drafted as part of our ongoing effort to heighten awareness of the need for information on the use of drugs in pediatric patients and transfer of that knowledge to product labeling. The checklist should be completed in the division and included in the action package for every new chemical entity recommended for approval. Although the checklist, as completed, will show the status of pediatric information at the time of preparation of the NDA action letter, completing it will require prior thought and action on the part of the reviewing division. In particular, for drugs that should be studied in pediatric patients after approval, the division will need to actively encourage the firm to conduct studies and to document the results of those discussions.

Robert Temple

Robert Temple, M.D.

James Bilstad

James Bilstad, M.D.

Attachment

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-727 Trade (generic) names B.D.I (hydralazine HCl + ISDN) Tabs

Check any of the following that apply and explain, as necessary, on the next page:

__1__ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

____ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

____ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

____ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)

____ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

____ a. The applicant has committed to doing such studies as will be required.

____ (1) Studies are ongoing.
____ (2) Protocols have been submitted and approved.
____ (3) Protocols have been submitted and are under review.
____ (4) If no protocol has been submitted, on the next page explain the status of discussions.

____ b. 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.

__X__ 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

____ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items: _____

Signature of Preparer

4/11/97
Date

cc: Orig NDA
HFD-___/Div File
NDA Action Package