CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 20-727

Chemistry Review(s)

NDA 20-727

BiDil®(isosorbide dinitrate and hydralazine HCl) Tablets

NitroMed, Inc.

Kris Raman, Ph.D.

Division of Cardio-Renal Drug Products (HFD-110)

Review of Chemistry, Manufacturing, and Controls

CHEMISTRY REVIEW

1. **NDA:** 20-727

2. **REVIEW:** # 6

3. **REVIEW DATE:** 6/21/05

4. **REVIEWER:** Kris Raman

5. **PREVIOUS DOCUMENTS:**

Previous Documents	Date
Original submission	7/3/1996
Review 1	8/14/1996
Review 2	11/7/1996
Review 3	3/24/1997
Review 4	4/10/02
Review 5	5/17/05
Resubmission amendment No. 119, NDA 20-727	11/24/04
Amendment	4/27/05

6. **SUBMISSION(S) BEING REVIEWED:**

Submissions(s) Reviewed	Date
Amendment	6/9/05

7. **NAME & ADDRESS OF APPLICANT:**

Name:	NitroMed, Inc.
Address:	125 Spring Street Lexington, MA 02421
Representative:	Michael Sabolinski, M.D.
Telephone:	781-266-4000
Fax:	781-274-8080

8. **DRUG PRODUCT NAME/CODE/TYPE**

   a) **Proprietary Name: BiDil®**
   b) **Non-Proprietary Name (USAN):** Isosorbide dinitrate and Hydralazine HCl
   c) **Code Name/# (ONDC only):**
      - **Chem. Type: 4**
      - **Submission Priority:** S

9. **LEGAL BASIS FOR SUBMISSION:** N/A

10. **PHARMACOL. CATEGORY:** Used in the treatment of heart failure

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 20/37.5 mg

13. ROUTE OF ADMINISTRATION: Oral

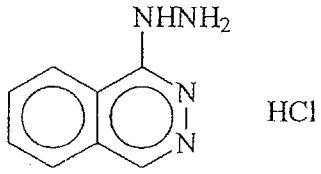
14. Rx/OTC DISPENSED: X **Rx** ____ **OTC**

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note 28]:

No

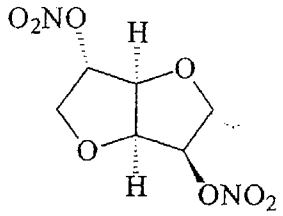
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Hydralazine HCl



Molecular Formula: $C_8H_9ClN_4$ Molecular Weight: 196.64

Isosorbide Dinitrate



Molecular Formula: $C_6H_8N_2O_8$
Molecular Weight: 236.14

RELATED/SUPPORTING DOCUMENT:

A. DMFS:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	II	[redacted]	Hydralazine hydrochloride	3	Adequate	J. Fan, Ph.D. 10/23/00	Drug substance
[redacted]	II	EMS-DOTTIKON	Diluted isosorbide dinitrate	3	Adequate	S. Saha, Ph.D 7/20/04	Drug substance
[redacted]	IV	[redacted]	OPADRY Orange, YS-1-6227	1	Adequate	K. Raman 4/18/05	Film coating system

[1] Action codes for DMF Table:
1 - DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 -Type 1 DMF
3 - Reviewed previously and no revision since last review
4 - Sufficient information in application
5 - Authority to reference not granted
6 - DMF not available
7 - Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	41,816	

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Acceptable	12/21/04	S. Adams (HFD-322)
Pharm/Tox	NA		
Biopharm	The recommended dissolution specification for BiDil tablet is: USP Apparatus 1 (basket), 100 rpm, 0.05N HCl 900 ml, 37°C ± 0.5°C, Q value NLT [redacted] in 30 minutes for both isosorbide dinitrate and hydralazine HCl.	4/15/05	Lydia Velaquez, Ph.D Peter Hinderling, Ph.D.
LNC	N/A	N/A	N/A
Methods Validation	Pending		
DMETS	DMETS does not recommend the use of the proprietary name 'BiDil' because the name will mislead the practitioner to believe the product is dosed twice daily. DMETS has no objection to the use of the proprietary name [redacted]. On April 1, 2005 Drs. Stockbridge and Temple discussed the tradename issue and decided that the recommended tradename would be 'BiDil'. DMETS has recommended implementation of the container labels and insert labeling revisions outlined in Section II of their review, dated 5/19/05, in order to minimize potential error.	 5/19/05	Laura Pincock, Pharm.D. Laura Pincock, Pharm.D.
EA	Acceptable, categorical exclusion has been granted as per information provided in this submission.	As per this review	Kris Raman, Ph.D.
Microbiology	N/A	N/A	N/A

N/A = Not Applicable

The Chemistry Review for NDA 20-727

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This resubmission of new drug application (NDA 20-727) may be '**Approved**' from the perspective of chemistry, manufacturing, and control. The firm should be reminded of their post approval commitments and additionally should continue to monitor the [ ] as an impurity/degradant in the release and stability testing of BiDil® tablets with a release/shelf life limit of NMT [ ]. The action letter should also state that BiDil® tablets have an expiration dating period of 6 months when stored at room temperature (25°C).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

BiDil® Tablet is a fixed dose combination formulation containing two active pharmaceutical ingredients, diluted isosorbide dinitrate, USP and hydralazine hydrochloride, USP. Hydralazine hydrochloride, USP is a peripheral vasodilator and diluted isosorbide dinitrate, USP an organic nitrate with vasodilator effects on both arteries and veins.

Both active ingredients, diluted isosorbide dinitrate, USP and hydralazine hydrochloride, USP, are available in the US as single agent brand and generic drug products. However, as single agents neither is indicated for the treatment of heart failure.

BiDil® Tablets are indicated for the treatment of heart failure in black patients, and will be marketed in the US by NitroMed, Inc. (Lexington, MA), the sponsor of this NDA. BiDil® Tablets will be marketed as an immediate release oral dosage form in the following strength:

BiDil® 20 (isosorbide dinitrate 20 mg/hydralazine HCl 37.5 mg) Tablets

In the original NDA submission (July 3, 1996) the prior NDA sponsor had

proposed four different strengths of BiDil® Tablets: 40/75, 20/75, 20/37.5, and 10/37.5 mg of isosorbide dinitrate and hydralazine HCl. However, in this NDA resubmission the current NDA sponsor NitroMed has proposed only one strength 20/37.5 mg of BiDil® Tablets in combination of isosorbide dinitrate and hydralazine HCl.

BiDil® (20/37.5 mg) Tablet is administered orally two tablets three times a day. Each tablet contains 20 mg isosorbide dinitrate and 37.5 mg hydralazine HCl. The tablet also contains anhydrous lactose, sodium starch glycolate, magnesium stearate, colloidal silicon, and Opadry Orange YS-1-6227 coating.

A formulation of BiDil® was initially developed by the prior sponsor of this NDA Medco Research, Inc., and the current sponsor of this NDA, NitroMed, Inc., continues to utilize the same formulation. The clinical and stability study batches were manufactured at Schwarz Pharma, Inc., the contract manufacturer for NitoMed. The commercial scale manufacturing process of BiDil® film coated tablet involves [ ] and finally coating of the tablets. BiDil® tablets are biconvex with approximately 8 mm diameter, scored, film-coated, orange tablets debossed 20 on one side over the score and N on the other side. The release and stability specifications for the clinical and stability lots are identical. The release and stability specifications for the commercial lots are same as for the clinical lots except for the impurities/degradants, which are specified for the commercial lots. Validated analytical methods were provided in the submission.

Based on dissolution profiles, a recommendation has been made to tighten the proposed dissolution acceptance criteria for isosorbide dinitrate (see page 46 for details). The limited stability data provided so far seem to support this recommendation.

BiDil® Tablets are packaged for commercial sale and physician sample in high density polyethylene (HDPE) bottles with heat induction sealed innerseals with child-resistant closures. [ ] The proposed market package will be 180-count tablets in 100 cc HDPE bottles. Other packaging sizes have been used in the stability studies, and all packaging containers have been composed of HDPE.

Both drug substances diluted isosorbide dinitrate and hydralazine HCl have USP monographs. Both drug substances are prepared synthetically. The isosorbide dinitrate is the subject of DMF [ ] and was found adequate for this NDA. Isosorbide dinitrate is manufactured by EMS-DOTTIKON at Dottikon, Switzerland facility. Isosorbide dinitrate is white to off-white crystalline powder with melting point 70 to 71°C. Because of explosive nature of isosorbide dinitrate

it is diluted with lactose and is referred to as diluted isosorbide dinitrate, USP. The hydralazine HCl is the subject of DMF [ ] and was found adequate for this NDA. Hydralazine HCl is manufactured by [ ]. Hydralazine HCl is white to off-white crystalline powder, melts with decomposition near 273°C. Batch analysis data of three batches of each isosorbide dinitrate and hydralazine HCl was submitted. Validated analytical methods were provided in the DMFs. A retest date of [ ] has been established for both bulk substances by the drug product contract manufacturer Schwarz Pharma.

NitroMed addressed all three CMC deficiencies, listed in the July 2, 1997 'Not-Approvable' action letter from the agency. The details of these responses have been discussed in the drug product section of this review.

B. Description of How the Drug Product is intended to be used

BiDil® drug product will be marketed in HDPE bottles in single strength of 20/37.5 mg of a combination of isosorbide dinitrate and hydralazine HCl. Treatment with BiDil is initiated at a dose of one BiDil® Tablet, 3 times a day. BiDil® may be titrated to maximum of two BiDil® Tablets, 3 times a day or to the maximum tolerated dose. Some patients may experience side effects and may take longer to reach their highest dose. The dosage may be decreased to as little as one-half BoDil® Tablet 3 times a day if intolerable side effects occur. The scoring on the tablet enables the patient to split the tablet into half.

NitroMed initially provided the stability for [ ] long term and [ ] at accelerated conditions for only one batch (# P425102) of 180-tablet count in 100 cc HDPE bottle commercial packaging. In the recent amendment, NitroMed has provided additional stability data up to 3 months on three validation batches packaged in 180-count 100 cc bottles commercial packaging. [ ] and [ ] data for two batches of [ ] packaging configuration.

A short **expiration dating period of 6 months** is assigned at this stage for BiDil® Tablets, when stored at room temperature (25°C), [ ] and 180-count/100 cc commercial packaging, because of uncertainties regarding the increase in formation of [ ] on extended storage.

The storage conditions for the drug product were recommended as "Store at 25°C (77°F), excursion permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature.]. Protect from light. Dispense in a light-resistant, tight container.

C. Basis for Approvability or Not-Approval Recommendation

The deficiencies identified in CMC review # 5 were resolved either with post approval commitments or satisfactory implementation of the agency's recommendation. The status and safety of the [ ] has not been yet established. However, by limiting this [ ] below the ICH threshold for qualification (NMT [ ] for both release and shelf life, there is assurance that the marketed product will not contain high levels of this impurity. A short expiration dating period of 6 months is also appropriate at this stage given the uncertainties regarding the increase in formation of this [ ] on extended storage as well as the ability to meet dissolution specifications recommended by OCPB.

NDA 20-727 for BiDil® (isosorbide dinitrate and hydralazine hydrochloride) may be '**Approved**' from CMC stand point.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: Kris Raman/6/21/05
Chemistry Team Leader: Kasturi Srinivasachar/6/21/05
Project Manager: Denise Hinton

C. CC Block

Original NDA 20-727
HFD-110/Division File
HFD-110/Team Leader/Kasturi Srinivasachar
HFD-810/Chemistry Division Director/John Simmons

19 Page(s) Withheld

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

____ § 552(b)(5) Deliberative Process

____ § 552(b)(4) Draft Labeling

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

/s/

Kris Raman
6/21/05 11:59:51 AM
CHEMIST

Kasturi Srinivasachar
6/21/05 12:04:22 PM
CHEMIST

NDA 20-727

BiDil®20 (isosorbide dinitrate and hydralazine HCl) Tablets

NitroMed, Inc.

Kris Raman, Ph.D.

Division of Cardio-Renal Drug Products (HFD-110)

Review of Chemistry, Manufacturing, and Controls

1. **NDA:** 20-727

2. **REVIEW:** # 5

3. **REVIEW DATE:** 5/17/05

4. **REVIEWER:** Kris Raman

5. **PREVIOUS DOCUMENTS:**

Previous Documents	Date
Original submission	7/3/1996
Review 1	8/14/1996
Review 2	11/7/1996
Review 3	3/24/1997
Review 4	4/10/02

6. **SUBMISSION(S) BEING REVIEWED:**

Submissions(s) Reviewed	Date
Resubmission amendment No. 119, NDA 20-727	11/24/04
Amendment	4/27/05

7. **NAME & ADDRESS OF APPLICANT:**

Name:	NitroMed, Inc.
Address:	125 Spring Street Lexington, MA 02421
Representative:	Michael Sabolinski, M.D.
Telephone:	781-266-4000
Fax:	781-274-8080

8. **DRUG PRODUCT NAME/CODE/TYPE**

   a) **Proprietary Name: BiDil®**
   b) **Non-Proprietary Name (USAN):** Isosorbide dinitrate and Hydralazine HCl
   c) **Code Name/# (ONDC only):**
      - **Chem. Type: 4**
      - **Submission Priority:** S

9. **LEGAL BASIS FOR SUBMISSION:** N/A

10. **PHARMACOL. CATEGORY:** Used in the treatment of heart failure

11. **DOSAGE FORM:** Tablets

RELATED/SUPPORTING DOCUMENT:

A. DMFS:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	II	[redacted]	Hydralazine hydrochloride	3	Adequate	J. Fan, Ph.D. 10/23/00	Drug substance
[redacted]	II	EMS-DOTTIKON	Diluted isosorbide dinitrate	3	Adequate	S. Saha, Ph.D 7/20/04	Drug substance
[redacted]	IV	[redacted]	OPADRY Orange, YS-1-6227	1	Adequate	K. Raman 4/18/05	Film coating system

[1] Action codes for DMF Table:
1 - DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 -Type 1 DMF
3 - Reviewed previously and no revision since last review
4 - Sufficient information in application
5 - Authority to reference not granted
6 - DMF not available
7 - Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	41,816	

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Acceptable	12/21/04	S. Adams (HFD-322)
Pharm/Tox	NA		
Biopharm	The recommended dissolution specification for BiDil tablet is: USP Apparatus 1 (basket), 100 rpm, 0.05N HCl 900 ml, 37± 0.5°C, Q value NLT [redacted] in 30 minutes for both isosorbide dinitrate and hydralazine HCl.	4/15/05	Lydia Velaquez, Ph.D Peter Hinderling, Ph.D.
LNC	N/A	N/A	N/A
Methods Validation	Pending		
DMETS	DMETS does not recommend the		Laura Pincock, Pharm.D.

	use of the proprietary name 'BiDil' because the name will mislead the practitioner to believe the product is dosed twice daily. DMETS has no objection to the use of the proprietary name '[ ]' On April 1, 2005 Drs. Stockbridge and Temple discussed the tradename issue and decided that the recommended tradename would be 'BiDil'. The 'Package Insert' consult request has been sent to DDMAC on 4/12/05		
EA	Acceptable, categorical exclusion has been granted as per information provided in this submission.	As per this review	Kris Raman, Ph.D.
Microbiology	N/A	N/A	N/A

N/A = Not Applicable

Appears This Way
On Original

The Chemistry Review for NDA 20-727

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This resubmission of new drug application (NDA 20-727) is '**Approvable**' from the perspective of chemistry, manufacturing, and control. A deficiency letter has been sent to the applicant outlining the information that is needed to complete this application. The deficiencies are detailed at the end of this review. The Office of Compliance has issued an overall acceptable recommendation for all establishments on 12/21/2004 (see attachment).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

BiDil® Tablet is a fixed dose combination formulation containing two active pharmaceutical ingredients, diluted isosorbide dinitrate, USP and hydralazine hydrochloride, USP. Hydralazine hydrochloride, USP is a peripheral vasodilator and diluted isosorbide dinitrate, USP an organic nitrate with vasodilator effects on both arteries and veins.

Both active ingredients, diluted isosorbide dinitrate, USP and hydralazine hydrochloride, USP, are available in the US as single agent brand and generic drug products. However, as single agents neither is indicated for the treatment of heart failure.

BiDil® Tablets are indicated for the treatment of heart failure in black patients, and will be marketed in the US by NitroMed, Inc. (Lexington, MA), the sponsor of this NDA. BiDil®20 Tablets are also sometimes referred to as BiDil® Tablets (20/37.5 mg). BiDil® Tablets will be marketed as an immediate release oral dosage form in the following strength:

BiDil® 20 (isosorbide dinitrate 20 mg/hydralazine HCl 37.5 mg) Tablets

In the original NDA submission (July 3, 1996) the prior NDA sponsor had proposed four different strengths of BiDil® Tablets: 40/75, 20/75, 20/37.5, and

10/37.5 mg of isosorbide dinitrate and hydralazine HCl. However, in this NDA resubmission the current NDA sponsor NitroMed has proposed only one strength 20/37.5 mg of BiDil® Tablets in combination of isosorbide dinitrate and hydralazine HCl.

BiDil® (20/37.5 mg) Tablet is administered orally two tablets three times a day. Each tablet contains 20 mg isosorbide dinitrate and 37.5 mg hydralazine HCl. The tablet also contains anhydrous lactose, sodium starch glycolate, magnesium stearate, colloidal silicon, and Opadry Orange YS-1-6227 coating.

A formulation of BiDil® 20 was initially developed by the prior sponsor of this NDA Medco Research, Inc., and the current sponsor of this NDA, NitroMed, Inc., continues to utilize the same formulation. The clinical and stability study batches were manufactured at Schwarz Pharm, Inc., the contract manufacturer for NitoMed. The commercial scale manufacturing process of BiDil®20 film coated tablet involves [ ] and finally coating of the tablets. BiDil® 20 tablets are biconvex with approximately 8 mm diameter, scored, film-coated, orange tablets debossed 20 on one side over the score and N on the other side. The release and stability specifications for the clinical and stability lots are identical. The release and stability specifications for the commercial lots are same as for the clinical lots except for the impurities/degradants, which are specified for the commercial lots. Validated analytical methods were provided in the submission.

Based on dissolution profiles, a recommendation has been made to tighten the proposed dissolution acceptance criteria for isosorbide dinitrate (see page 46 for details). The limited stability data provided so far seem to support this recommendation.

BiDil® 20 Tablets are packaged for commercial sale and physician sample in high density polyethylene (HDPE) bottles with heat induction sealed innerseals with child-resistant closures. [ ]. The proposed market package will be 180-count tablets in 100 cc HDPE bottles. Other packaging sizes have been used in the stability studies, and all packaging containers have been composed of HDPE.

Both drug substances diluted isosorbide dinitrate and hydralazine HCl have USP monographs. Both drug substances are prepared synthetically. The isosorbide dinitrate is the subject of DMF [ ] and was found adequate for this NDA. Isosorbide dinitrate is manufactured by EMS-DOTTIKON at Dottikon, Switzerland facility. Isosorbide dinitrate is white to off-white crystalline powder with melting point 70 to 71°C. Because of explosive nature of isosorbide dinitrate it is diluted with lactose and is referred to as diluted isosorbide dinitrate, USP. The hydralazine HCl is the subject of DMF [ ] and was found adequate for this NDA. Hydralazine HCl is manufactured by [ ] Hydralazine HCl is white to off-white crystalline powder,

melts with decomposition near 273°C. Batch analysis data of three batches of each isosorbide dinitrate and hydralazine HCl was submitted. Validated analytical methods were provided in the DMFs. A retest date of [ ] has been established for both bulk substances by the drug product contract manufacturer Schwarz Pharma.

NitroMed addressed two of three CMC deficiencies, listed in the July 2, 1997 'Not-Approvable' action letter from the agency, satisfactorily. However, one deficiency is still a pending issue. The details of these responses have been discussed in the drug product section of this review.

B. Description of How the Drug Product is intended to be used

BiDil® drug product will be marketed in HDPE bottles in single strength of 20/37.5 mg of a combination of isosorbide dinitrate and hydralazine HCl. Treatment with BiDil is initiated at a dose of one BiDil 20 Tablet, 3 times a day. BiDil may be titrated to maximum of two BiDil 20 Tablets, 3 times a day or to the maximum tolerated dose. Some patients may experience side effects and may take longer to reach their highest dose. The dosage may be decreased to as little as one-half BiDil 20 Tablet 3 times a day if intolerable side effects occur. The scoring on the tablet enables the patient to split the tablet into half.

NitroMed initiated the stability study on only one batch (# P425102) of 180-tablet count in 100 cc HDPE bottle commercial packaging. The applicant has provided the stability for [ ] long term and [ ] at accelerated conditions for only one batch (# P425102) of 180-tablet count in 100 cc HDPE bottle commercial packaging. [

]

Based on limited stability data on physician sample sizes, the requested expiration dating of [ ] cannot be granted at this time, however a [ ] expiration date for [ ] sample and [ ] expiration date [ ] sample is recommended. Because of inadequate stability data to support the 180-count commercial packaging, the requested [ ] expiration dating cannot be granted at this time, unless sufficient real time stability data at least on three batches is submitted.

The storage conditions for the drug product were recommended as "Store at 25°C (77°F), excursion permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature.]. Protect from light. Dispense in a light-resistant, tight container.

C. Basis for Approvability or Not-Approval Recommendation

NDA 20-727 for BiDil® 20 (isosorbide dinitrate and hydralazine hydrochloride) is **'Approvable'** from CMC stand point because of deficiencies related to drug substance and drug product, which are detailed at the end of this review. 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.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: Kris Raman/5/17/05
Chemistry Team Leader: Kasturi Srinivasachar/5/17/05
Project Manager: Denise Hinton

C. CC Block

Original NDA 20-727
HFD-110/Division File
HFD-110/Team Leader/Kasturi Srinivasachar
HFD-810/Chemistry Division Director/John Simmons

70 Page(s) Withheld

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

____ § 552(b)(5) Deliberative Process

____ § 552(b)(4) Draft Labeling

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

/s/

Kris Raman
5/17/05 08:37:58 AM
CHEMIST

Kasturi Srinivasachar
5/17/05 06:42:24 PM
CHEMIST

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-727 **DATE REVIEWED:** 04/10/02

REVIEW #: 04 **REVIEWER:** JV Advani

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL SUBMISSION	03-July-1996	08-July-1996	09-July-1996
AMENDMENT (BC)	26-Sep-1996	27-Sep-1996	01-Oct-1996
AMENDMENT (BC)	12-Dec-1996	13-Dec-1996	16-Dec-1996
Validation results reports	14-Mar-1997	19-Mar-1997	27-Oct-1996 (dist. Lab)
Amendment (BZ)	08-Jan-2001	10-Jan-2001	20-Jan-2001
Amendment (BZ)	20-Nov-2001	21-Nov-2001	26-Nov-2001

NAME & ADDRESS OF APPLICANT: NitroMed, Inc.
12 Oak Park Drive
Bedford, MA 01730

DRUG PRODUCT NAME

Proprietary: BiDil tablets
Established/USAN: Hydralazine HCl USP & Isosorbide Dinitrate USP
Code Name/#:
Chem.Type/Ther.Class: 4
CAS Registry Number 304-20-1 & 87-33-2

PHARMACOL. CATEGORY/INDICATION: Treatment of Congestive Heart Failure in patients intolerant to ACE Inhibitors

DOSAGE FORM: Tablets (film coated)
STRENGTHS: 37.5/20 in combination of Hydralazine HCl and isosorbide dinitrate

ROUTE OF ADMINISTRATION: Oral
Rx/OTC: _x_ Rx ___ OTC
PATENT STATUS: U.S. Patent # 4,868,179
SPECIAL PRODUCTS: ___ Yes _x_ No
(If yes, fill out the form for special products and deliver to TIA through team leader for data entry)

STRUCTURAL FORMULA, CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Names: 1(2H)-Phthalazinone hydrazone monohydrochloride and
1, 4, 3, 6-dianhydro-D-glucitol-2, 5-dinitrate.

Molecular Formula $C_8H_9ClN_4$ **Hydralazine** **Molecular weight** **160.18**
$C_6H_8N_2O_8$ **Isosorbide** **236.14**

[ ]

SUPPORTING DOCUMENTS: DMF [ ] DMF [ ] & also refer to review #1

RELATED DOCUMENTS (if applicable): IND 41,816
Submitted for BiDil Tablets by Medco Research, Inc.

CONSULTS: None

REMARKS:

BiDil contains hydralazine hydrochloride, USP, a peripheral vasodilator with antihypertensive properties, and diluted isosorbide dinitrate, USP, an organic nitrate with vasodilator effects on both arteries and veins. BiDil is a oral combo, intended for the treatment of chronic congestive heart failure as an adjunct to standard therapy (digitals glycosides and diurectics) in patients who are intolerant or have a contraindication to angiotensin-converting enzyme (ACE) inhibitors.
BiDil will be used in fixed combinations of tablets for oral administration.

The amendment of 08 Jan. 01 provides some of the responses to deficiencies noted in my Review #1 and also items discussed with the applicant in teleconference meeting on January 8 & 23, 2001. Applicant has submitted the updated specifications for the components to be consistent with USP 24, NF 19 and manufacturer's Schwarz Pharm, in house specifications. Also reference is made to Biopharm questions that were acceptable and revised proposed text for use in the labeling. The revised draft labeling is provided.

This amendment of 20 Nov. 01 provides responses to the CMC questions with supporting data.These responses were also discussed in a tele teleconference meeting on 01/23/01 (refer minutes dated 01/25/01).

CONCLUSIONS & RECOMMENDATIONS:

Applicant has provided the satisfactory requested information in recent amendments. This Constitute a complete response to the Non-Approvable letter of July 2, 1997 at this juncture.
When this submission is reviewed for approval, applicant will be asked to:

1) Review the LNC unacceptable proposed proprietary (refer review #3) BIDIL name. New proposed name will be sent out to OPDRA at that stage.
2) Submit the pharm/tox data on studies of pthalazine and phthalazinone degradants
3) Provide revised Methods Validation Package including stress studies data for district laboratories.

JV Advani, Review Chemist

5 Page(s) Withheld

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

____ § 552(b)(5) Deliberative Process

____ § 552(b)(4) Draft Labeling

J. Adyani
MAR 24 1997

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #:20-727 CHEM.REVIEW #:3 REVIEW DATE:03/20/97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	3-July-1996	08-July-1996	09-July-1996
Amendment BC	26-Sep-1996	27-Sep-1996	01-Oct-1996
Amendment BC	**12-Dec-1996**	**13-Dec-1996**	**16-Dec-1996**
Validation results reports	**14-Mar-1997**	**19-Mar-1997**	**27-Oct-1996 (dist. Lab)**

NAME & ADDRESS OF APPLICANT: Medco Research, Inc.
85 T.W. Alexander Drive
Research Triangle Park, North Carolina 27709

DRUG PRODUCT NAME:
Proprietary: **BiDil** tablets
Nonproprietary/USAN: Hydralazine HCl USP & Isosorbide Dinitrate USP
Code Name/#:
Chemical Abstracts Services (CAS) Registry number 304-20-1 & 87-33-2
Chem.Type/Ther.Class: 4

PATENT STATUS:

US Patent No.	Expiration Date	Assignee	Product
4,868,179	April 22, 2007	Jay B. Cohn, MD Medco research, Inc.	Bidil

PHARMACOL.CATEGORY/INDICATION: **Treatment of Congestive Heart Failure in patients intolerant to ACE Inhibitors.**

DOSAGE FORM: Tablets (film coated)

STRENGTHS: 75/40, 75/20, 37.5/20, 37.5/10 in combination of hydralazine HCl and isosorbide dinitrate.

ROUTE OF ADMINISTRATION: Oral

DISPENSED: __x__ Rx _____ OTC

STRUCTURAL FORMULA, CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemically, 1(2H)-Phthalazinone hydrazone monohydrochloride and 1,4,3,6-dianhydro-D-glucitol-2,5-dinitrate.

Empirical formula:		Molecular Weight:	
Hydralazine	**$C_8H_9ClN_4$** &	**Hydralazine**	**160.18**
Isosorbide	**$C_6H_8N_2O_8$**	**Isosorbide**	**236.14**

These two drug substances Isosorbide and Hydralazine have been comprehensively described by Silvieri, De Angelis and Orzech, Nash and Daley in "Analytical Profiles of Drug Substances" (Florey 4, 225-244, & 8, 283-314).

SUPPORTING DOCUMENTS:
IND 41,816 - BiDil Tablets, Medco Research, Inc.
DMF [ ] - Sumika Fine Chemical Co., Ltd. Type II (Hydralazine Drug Substance). NDA review is relied on previous review of Kathleen Jongedyke.
DMF [ ] - EMS-Dottikon AG, Type II (Drug Substance). This DMF is reviewed on 8/96.
DMF [ ] -
DMF -
DMF -
DMF -
DMF -

RELATED DOCUMENTS (if applicable):
NDA 8-303 - Apresoline HCl, Ciba-Geigy Corp.
- Isordil, Wyeth-Ayerst Labs. (Isosorbide dinitrate)

CONSULTS: None

REMARKS/COMMENTS:
BiDil contains hydralazine hydrochloride, USP, a peripheral vasodilator with antihypertensive properties, and diluted isosorbide dinitrate, USP, an organic nitrate with vasodilator effects on both arteries and veins. BiDil is a oral combo, intended for the treatment of chronic congestive heart failure as an adjunct to standard therapy (digitals glycosides and diuretics) in patients who are intolerant or have a contraindication to angiotensin-converting enzyme (ACE) inhibitors.
This amendment BC of 9/26/96 provides a response to requests for information related to Chemist's Review #1.
BiDil will be used in fixed combinations of tablets for oral administration.
The trademark was sent to the Labeling and Nomenclature Committee (LNC) for comments. The LNC finds the proposed proprietary BIDIL name unacceptable as BID an abbreviation for the Latin instruction of "twice daily" could be potentially misleading and confusing.
EER was requested on 07/25/96
This amendment BC of 12/12/96 provides a response to requests for information related to Chemist's Review #2.
The methods validation was requested on 9/12/96 from two laboratories and Cincinnati laboratory results are reported.
CONCLUSIONS & RECOMMENDATIONS:
Firm has done no original animal studies on the BiDil drug product. The firm has done a literature/FOI review of available data on hydralazine and ISDN. It is therefore, necessary for the firm to evaluate the possibility of an interaction between the drug substances (as the secondary & tertiary amines react with the nitrous acid in acidic conditions to form N-nitrosoamines) and evaluate the pharmacological and/or toxicity of the reaction product. Applicant states that all related substances formed on stability at levels [ ], will be monitored for pharmacology and toxicity. N-Nitroamines like compounds are carcinogenic, we therefore recommend that these related compounds be examined at lower than [ ] levels.

DMF [ ] Type II for ISDN has been reviewed by me, there is no stability data on the drug substance. EMS-Dottikon AG has indicated that stability data on the ISDN-[ ] will be submitted soon but the data is not received as yet.
Additional information on related substances and thermal degradation products is requested.
Results from validation data package from Cincinnati district laboratory has been received on 03/19/97. They have encounter the problem with firm's assay-ID-related compounds method, [ ]. One extra large peak is found that is not identified and the [ ] for the compounds are significantly different than the one shown in the method. The results indicate the method [ ] is not suitable for regulatory control of this product. The product did not meet the firm's specifications for impurities testing limits NMT [ ] The method submitted by the firm is not acceptable for the regulatory purpose.

Not Approvable
cc:
Orig. NDA
HFD-110/Division File
HFD-110/JAdvani/ 03/21/97
HFD-110/CSO
District

J.V. Advani, Review Chemist
filename: **N20727-3**

R/D Init by: RWolters/

3.12.97

3 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

G. Buehler

NOV 7 1996

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #:20-727 CHEM.REVIEW #:2 REVIEW DATE:10/31/96

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	3-July-1996	08-July-1996	09-July-1996
Amendment BC	**26-Sep-1996**	**27-Sep-1996**	**01-Oct-1996**

NAME & ADDRESS OF APPLICANT: Medco Research, Inc.
85 T.W. Alexander Drive
Research Triangle Park, North Carolina 27709

DRUG PRODUCT NAME:

Proprietary: **BiDil** tablets
Nonproprietary/USAN: Hydralazine HCl USP & Isosorbide Dinitrate USP
Code Name/#:
Chemical Abstracts Services (CAS) Registry number 304-20-1 & 87-33-2
Chem.Type/Ther.Class: 4

PATENT STATUS:

US Patent No.	Expiration Date	Assignee	Product
4,868,179	April 22, 2007	Jay B. Cohn, MD Medco research, Inc.	Bidil

PHARMACOL.CATEGORY/INDICATION: **Treatment of Congestive Heart Failure in patients intolerant to ACE Inhibitors.**

DOSAGE FORM: Tablets (film coated)

STRENGTHS: 75/40, 75/20, 37.5/20, 37.5/10 in combination of hydralazine HCl and isosorbide dinitrate.

ROUTE OF ADMINISTRATION: Oral

DISPENSED: __x__ Rx _____ OTC

STRUCTURAL FORMULA, CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemically, 1(2H)-Phthalazinone hydrazone monohydrochloride and 1,4,3,6-dianhydro-D-glucitol-2,5-dinitrate.

Empirical formula:			Molecular Weight:	
Hydralazine	**$C_8H_9ClN_4$**	**&**	**Hydralazine**	**160.18**
Isosorbide	**$C_6H_8N_2O^8$**		**Isosorbide**	**236.14**

These two drug substances Isosorbide and Hydralazine have been comprehensively described by Silvieri, De Angelis and Orzech, Nash and Daley in "Analytical Profiles of Drug Substances" (Florey 4, 225-244, & 8, 283-314).

SUPPORTING DOCUMENTS:
IND 41,816 - BiDil Tablets, Medco Research, Inc.
DMF [ ] - Sumika Fine Chemical Co., Ltd. Type II (Hydralazine Drug Substance). NDA review is relied on previous review of Kathleen Jongedyke.
DMF [ ] - EMS-Dottikon AG, Type II (Drug Substance). This DMF is reviewed on 8/96.
DMF [ ] -
DMF [ ] -
DMF [ ] -
DMF [ ] -
DMF [ ] -

RELATED DOCUMENTS (if applicable):
NDA 8-303 - Apresoline HCl, Ciba-Geigy Corp.
- Isordil, Wyeth-Ayerst Labs. (Isosorbide dinitrate)

CONSULTS: None

REMARKS/COMMENTS:
BiDil contains hydralazine hydrochloride, USP, a peripheral vasodilator with antihypertensive properties, and diluted isosorbide dinitrate, USP, an organic nitrate with vasodilator effects on both arteries and veins. BiDil is a oral combo, intended for the treatment of chronic congestive heart failure as an adjunct to standard therapy (digitals glycosides and diurectics) in patients who are intolerant or have a contraindication to angiotensin-converting enzyme (ACE) inhibitors.
This amendment BC of 9/26/96 provides a response to requests for information related to Chemist's Review #1.
BiDil will be used in fixed combinations of tablets for oral adminstration. The trademark was sent to the Labeling and Nomenclature Committee (LNC) for comments. **The LNC finds the proposed proprietary BIDIL name unaceeptable as BID an abbreviation for the Latin instruction of "twice daily" could be potentially misleading and confusing.**

CONCLUSIONS & RECOMMENDATIONS:
Firm has done no original animal studies on the BiDil drug product. The firm has done a literature/FOI review of available data on hydralazine and ISDN. It is therefore, necessary for the firm to evaluate the possibilty of an interaction between the drug substances (as the secondary & tertiary amines react with the nitrous acid in acidic conditions to form N-nitrosoamines) and evaluate the pharmacological and/or toxicity of the reaction product.
Applicant states that all related substances formed on stability at levels [ ] will be monitored for pharmacology and toxicity. N-Nitroamines like compounds are carcinogenic, we therefore recommend that these related compounds be examined at [redacted] lower than [ ] levels.

DMF [ ] Type II for Hydralazine hydrochloride is reviewed by Kathleen Jongedyke on 2/16/96 and 4/30/96.
DMF [ ] Type II for ISDN has been reviewed by me, there is no stability data on the drug substance. EMS-Dottikon AG has indicated that stability data on the ISDN- [ ] will be submitted soon.
Additional information on related substances and thermal degradation products is requested. Also there are typographic errors in the stability tables in attachment VI of this submission, these will be conveyed to the firm in the telephone conversation.
cc:
Orig. NDA
HFD-110/Division File
HFD-110/JAdvani/ 11/05/96
HFD-110/CSO
District

R/D Init by: RWolters/

J.V. Advani, Review Chemist
filename: **N20727**

rwolt 11/7/96

6 Page(s) Withheld

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

____ § 552(b)(5) Deliberative Process

____ § 552(b)(4) Draft Labeling

BUEHLER

AUG 14 1996

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #:20-727 **CHEM.REVIEW #:**1 **REVIEW DATE:**08/12/96

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	3-July-1996	08-July-1996	09-July-1996

NAME & ADDRESS OF APPLICANT: Medco Research, Inc.
85 T.W. Alexander Drive
Research Triangle Park, North Carolina 27709

DRUG PRODUCT NAME:
Proprietary: **BiDil** tablets
Nonproprietary/USAN: Hydralazine HCl USP & Isosorbide Dinitrate USP
Code Name/#:
Chemical Abstracts Services (CAS) Registry number 304-20-1 & 87-33-2
Chem.Type/Ther.Class: 4

PATENT STATUS:

US Patent No.	Expiration Date	Assignee	Product
4,868,179	April 22, 2007	Jay B. Cohn, MD Medco research, Inc.	Bidil

PHARMACOL.CATEGORY/INDICATION: **Treatment of Congestive Heart Failure in patients intolerant to ACE Inhibitors.**

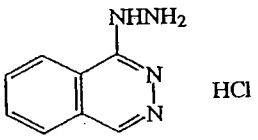
DOSAGE FORM: Tablets (film coated)

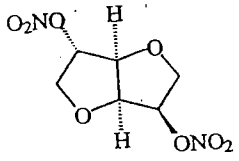
STRENGTHS: 75/40, 75/20, 37.5/20, 37.5/10 in combination of hydralazine HCl and isosorbide dinitrate.

ROUTE OF ADMINISTRATION: Oral

DISPENSED: __x__ **Rx** _____ **OTC**

STRUCTURAL FORMULA, CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT:





Chemically, 1(2H)-Phthalazinone hydrazone monohydrochloride and 1,4,3,6-dianhydro-D-glucitol-2,5-dinitrate.

Empirical formula:			Molecular Weight:	
Hydralazine	$C_8H_9ClN_4$	&	**Hydralazine**	**160.18**
Isosorbide	$C_6H_8N_2O^8$		**Isosorbide**	**236.14**

These two drug substances Isosorbide and Hydralazine have been comprehensively described by Silvieri, De Angelis and Orzech, Nash and Daley in "Analytical Profiles of Drug Substances" (Florey 4, 225-244, & 8, 283-314).

SUPPORTING DOCUMENTS:
IND 41,816 - BiDil Tablets, Medco Research, Inc.
DMF [ ] - Sumika Fine Chemical Co., Ltd. Type II (Hydralazine Drug Substance). NDA review is relied on previous review of Kathleen Jongedyke.
DMF [ ] - EMS-Dottikon AG, Type II (Drug Substance). This DMF is reviewed on 8/96.
DMF - [ ]
DMF - [ ]
DMF - [ ]
DMF - [ ]
DMF - [ ]
DMF

RELATED DOCUMENTS (if applicable):
NDA 8-303 - Apresoline HCl, Ciba-Geigy Corp.
- Isordil, Wyeth-Ayerst Labs. (Isosorbide dinitrate)

CONSULTS: None

REMARKS/COMMENTS:
BiDil contains hydralazine hydrochloride, USP, a peripheral vasodilator with antihypertensive properties, and diluted isosorbide dinitrate, USP, an organic nitrate with vasodilator effects on both arteries and veins. BiDil is a oral combo, intended for the treatment of chronic congestive heart failure as an adjunct to standard therapy (digitals glycosides and diurectics) in patients who are intolerant or have a contraindication to angiotensin-converting enzyme (ACE) inhibitors.
BiDil will be used in fixed combinations of tablets for oral adminstration. The trademark was sent to the Labeling and Nomenclature committee for comments.

CONCLUSIONS & RECOMMENDATIONS:
Firm has done no original animal studies on the BiDil drug product. The firm has done a literature/FOI review of available data on hydralazine and ISDN. It is therefore, necessary for the firm to evaluate the possibilty of an interaction between the drug substances (as the secondary & tertiary amines react with the nitrous acid in acidic conditions to form N-nitrosoamines) and evaluate the pharmacological and/or toxicity of the reaction product.

DMF [ ] Type II for Hydralazine hydrochloride is reviewed by Kathleen Jongedvke on 2/16/96 and 4/30/96.
DMF [ ] Type II for ISDN has been reviewed by me, there is no stability data on the drug substance. We will write to EMS-Dottikon AG to provide stability data on the ISDN [ ]

Also additional information is requested from the Medco Research.

cc:
Orig. NDA
HFD-110/Division File
HFD-110/JAdvani/ 08/12/96
HFD-110/CSO
District

R/D Init by: RWolters/

J.V. Advani, Review Chemist
filename: **N20727**

8/14/96

21 Page(s) Withheld

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

____ § 552(b)(5) Deliberative Process

____ § 552(b)(4) Draft Labeling