



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

US Patent No.: 4,868,179

Issue Date: September 19, 1989

Application No.: 07/041,210

Application Filing Date: April 22, 1987

Inventor: Jay N. Cohn

Title: Method of Reducing Mortality Associated with Congestive
Heart Failure Using Hydralazine and Isosorbide Dinitrate

Mail Stop Patent Ext.

Commissioner for Patents

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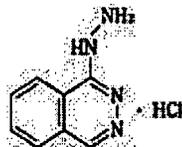
Application for Extension of Patent Term under 35 U.S.C. § 156 and 37 C.F.R. § 1.740

Sir:

Pursuant to the requirements of 35 U.S.C. § 156 and 37 CFR § 1.740, this application for extension of US Patent No. 4,868,179 is being made to the Director.

(1) The trade name for the approved product is BiDil[®]. A BiDil[®] Tablet contains a fixed dose combination of 37.5 mg hydralazine hydrochloride and 20 mg isosorbide dinitrate. A copy of the FDA approved package insert prepared by NitroMed, Inc., the NDA holder, is attached as Appendix A.

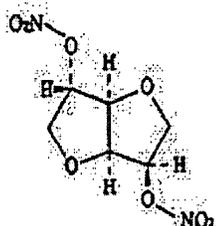
The chemical name for hydralazine hydrochloride is 1-hydrazinophthalazine monohydrochloride. The compound has an empirical formula of $C_8H_8N_4 \cdot HCl$, and a molecular weight of 196.64. Hydralazine hydrochloride has the following structural formula:



The chemical name for isosorbide dinitrate is 1,4:3,6-dianhydro-D-glucitol 2,5-dinitrate.

The compound has an empirical formula of $C_6H_8N_2O_8$, and a molecular weight of 236.14.

Isosorbide dinitrate has the following structural formula:



- (2) BiDil[®] is a new human drug for the treatment of heart failure. Consequently, the testing phase of the regulatory review of BiDil[®] occurred under subsection 505(i) (1993-1996) of the Federal Food, Drug, and Cosmetic Act (FFDCA). 35 U.S.C. § 156(g) (1)(B)(i) (2005). The NDA phase of BiDil[®]'s regulatory review occurred under FFDCA 505(c) (1996-2005). 35 U.S.C. § 156(g) (1)(B)(ii) (2005).
- (3) BiDil[®] was approved by the Food and Drug Administration (FDA) on June 23, 2005. A copy of the approval letter is attached as Appendix B.
- (4) The active ingredients in BiDil[®] are hydralazine hydrochloride and isosorbide dinitrate.

Hydralazine hydrochloride has not been previously studied under FFDCA § 505(i) (1993-1996), and has not been previously approved for commercial marketing or use under FFDCA § 505(c) (1996-2005). According to the attached list¹ (Appendix C) provided by the FDA, hydralazine hydrochloride new drug applications (NDAs) became effective for use in the treatment of hypertension under a different provision of law, FFDCA § 505(c) (1952-1962). Further according to the list, Abbreviated New Drug Applications (ANDAs) for hydralazine hydrochloride also were approved under different provisions of law, FFDCA § 505(c) (1974-

¹ The list was generated in response to a Freedom of Information Act request, and is dated September 9, 2004. With the exception of BiDil[®], FDA's Orange Book lists no hydralazine hydrochloride or isosorbide dinitrate approvals after that date.

1984), and FFDCA § 505(j) (1984-2001). Side-by-side comparison of the statutory provisions makes clear that the other hydralazine products did not receive permission for commercial marketing under “the provision of law under which [BiDil[®]’s] regulatory review period occurred”. 35 U.S.C. § 156(g)(a)(5)(A).

Patent term restoration for combination products, of course, is allowed if at least one of the active ingredients meets the standards therefore. 35 U.S.C. 156(f)(1)-(2). Thus, BiDil[®] is eligible for patent term restoration on the basis of its hydralazine hydrochloride component alone. However, a similar, albeit incomplete, history obtains with respect to isosorbide dinitrate, BiDil[®]’s other active ingredient. According to the attached list, until BiDil[®], isosorbide dinitrate had not been previously approved under FFDCA § 505(c) (November 21, 1997-2005). Early isosorbide dinitrate NDAs were approved for angina under FFDCA § 505(c) (1961). Subsequently, a number of NDAs and ANDAs entered the market. Without access to additional, potentially confidential and/or lost information, it is difficult to infer anything more about the isosorbide dinitrate products on the list.

(5) This application is being submitted within the sixty (60) day period permitted for submission pursuant to 37 CFR § 1.720(f). BiDil[®] first received permission for commercial marketing or use on June 23, 2005. The date of the last day on which this application could be submitted is August 22, 2005.

(6) An extension is being sought for US Patent No. 4,868,179. The inventor is Jay N. Cohn. The patent issued on September 19, 1989. The patent expiration date is April 22, 2007.

(7) A copy of US Patent No. 4,868,179, including the entire specification is attached hereto as Appendix D.

(8) A copy of the maintenance fee payment receipts for the payment years 4, 8, and 12 are attached hereto as Appendix E. No disclaimers, certificates of correction or reexamination certificates are associated with US Patent No. 4,868,179.

(9) US Patent No. 4,868,179 claims a method of using BiDil[®], i.e., the approved product.

The following table lists each applicable patent claim and demonstrates (e.g., in bold italics) the manner in which the patent claims read on the method of using the approved product.

US Patent No. 4,868,179	FDA-Approved Package Insert for BiDil [®]
<p><i>Claim 1</i></p> <p>A method of reducing the incidence of mortality associated with chronic congestive heart failure in a patient with impaired cardiac function and concomitant reduced exercise tolerance, comprising the oral administration to said patient in need of the same of a combination of (a) between about 75 and about 300 milligrams of hydralazine, or a pharmaceutically acceptable acid addition salt² thereof, per day, and (b) between about 40 and about 160 milligrams of isosorbide dinitrate, per day.</p>	<p>Indications and Usage</p> <p><i>BiDil is indicated for the treatment of heart failure as an adjunct to standard therapy in self-identified black patients to improve survival, to prolong time to hospitalization for heart failure, and to improve patient-reported functional status. There is little experience in patients with NYHA class IV heart failure. Most patients in the clinical trial supporting effectiveness (A-HeFT) received a loop diuretic, an angiotensin converting enzyme inhibitor or an angiotensin II receptor blocker, and a beta blocker, and many also received a cardiac glycoside or an aldosterone antagonist.</i></p> <p>Description</p> <p><i>Each BiDil Tablet for oral administration contains 20 milligrams of isosorbide dinitrate and 37.5 milligrams of hydralazine hydrochloride.</i></p> <p>Dosage and Administration</p> <p><i>Treatment with BiDil should be initiated at a dose of one BiDil Tablet, 3 times a day. BiDil may be titrated to a maximum tolerated dose, not to exceed two BiDil Tablets, 3 times a day.</i></p>

² The specification of U.S. Patent No. 4,868,179 states that the hydrochloride salt is the preferred "pharmaceutically acceptable acid additional salt." Col. 3, lines 19-21.

US Patent No. 4,868,179	FDA-Approved Package Insert for BiDil®
<p><i>Claim 2</i></p> <p>A method according to claim 1, wherein said patient is further treated orally with digoxin in an amount sufficient to achieve in said patient a blood serum concentration of digoxin³ of at least about 0.7 nanograms per milliliter and an effective edema managing amount of a pharmaceutically acceptable diuretic selected from the group consisting of thiazides, ethacrynic acid, furosemide, spironalactone and triamterene.</p>	<p>Indications and Usage</p> <p>BiDil is indicated for the treatment of heart failure <i>as an adjunct to standard therapy</i> in self-identified black patients to improve survival, to prolong time to hospitalization for heart failure, and to improve patient-reported functional status. There is little experience in patients with NYHA class IV heart failure. <i>Most patients in the clinical trial supporting effectiveness (A-HeFT) received a loop diuretic</i>, an angiotensin converting enzyme inhibitor or an angiotensin II receptor blocker, and a beta blocker, and <i>many also received a cardiac glycoside</i> or an aldosterone antagonist.</p>

³ Digoxin is a known cardiac glycoside. Two suppliers of digoxin tablets, Mylan Bertek Pharmaceuticals, Inc. and GlaxoSmithKline, both list the following information in the 2005 Physician's Desk Reference, under "Dosage and Administration, Serum Digoxin Concentrations" for their products, Digitek® and Lanoxin®: "About two-thirds of adults considered adequately digitalized (without evidence of toxicity) have serum digoxin concentrations ranging from 0.8 to 2.0 ng/mL. However, digoxin may produce clinical benefits even at serum concentrations below this range."

(10) The relevant dates and information pursuant to 35 USC § 156(g) are being provided to enable the Secretary of Health and Human Services to determine the applicable regulatory review period for BiDil[®]:

IND number 41,186 was effective April 1, 1993.

NDA number 20-727 was submitted on July 3, 1996.

The NDA for BiDil[®] was approved on June 23, 2005.

(11) A brief description of the activities undertaken during the applicable regulatory review period, and the dates applicable to such activities, between the U.S. Food and Drug Administration and the Applicant in IND 41,186 and NDA 20-727 is attached hereto as Appendix F.

(12) It is the opinion of NitroMed, Inc. that US Patent No. 4,868,179 is eligible for a 5-year period of extension of time. This period of extension was calculated in accordance with 37 CFR 1.775 as follows:

- (a) The regulatory review period under 35 USC 156(g)(1)(B) began on April 1, 1993 (the effective date of the IND) and ended on June 23, 2005 (the date of approval), amounting to a total of 4,466 days, which is the sum of (i) and (ii) below:
 - (i) The period of review under 35 USC 156(g)(1)(B)(i), the “testing period,” began on April 1, 1993 and ended on July 3, 1996, which equals 1,189 days.
 - (ii) The period of review under 35 USC 156(g)(1)(B)(ii), the “NDA period,” began on July 3, 1996 and ended on June 23, 2005, which equals 3,277 days.
- (b) The period for extension is calculated as the regulatory review period less:
 - (i) The number of days in the regulatory review period which were on or before the date on which the patent issued (September 19, 1989), i.e., 0 days, and
 - (ii) The number of days in which the Applicant did not act with due diligence, i.e., 0 days, and
 - (iii) One-half the number of days remaining in the period in the “testing period” after subtracting (i) and (ii) above, which is one-half of $(1,189 - [0 + 0])$ or 594 days

which results in a period of $4,466 - [0 + 0 + 594] = 3,872$ days.

- (c) 3,872 days when added to the original patent expiration date of April 22, 2007 would result in the date of August 29, 2017.
- (d) Fourteen years when added to the date of NDA approval (June 23, 2005) would result in the date of June 23, 2019.
- (e) The earlier date of (c) and (d) is August 29, 2017.
- (f) Since the patent at issue was issued after September 24, 1984, the extension is limited to no more than 5 years. Five years added to the original expiration date of April 22, 2007 results in the date April 22, 2012.
- (g) The earlier date of (e) and (f) is April 22, 2012.

Therefore, the extended expiration date of the subject patent is believed to be April 22, 2012, or an extension of 5 years (1,827 days).

(13) NitroMed acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension being sought.

(14) The Director is hereby authorized to charge the amount of \$1,120 to Deposit Account No. 08-0219 for receiving and acting upon this application for extension.

(15) All inquiries and correspondence relating to this application for patent term extension are to be directed to:

Michael Sabolinski, M.D.
Senior Vice President
Clinical Development and Regulatory Affairs
NitroMed, Inc.
125 Spring Street
Lexington, MA 02421
Telephone: (781) 266-4179
Fax: (781) 274-8080

This application is being submitted to the U.S. Patent Office in triplicate.

Also submitted is an Appointment of Agent to NitroMed, Inc., duly signed by Jay N. Cohn (the owner of U.S. Patent No. 4,868,179) and a Power of Attorney signed by NitroMed, Inc. (the licensee under the subject patent).

Respectfully submitted,

Date: August 19, 2005

By: Hollie L. Baker
Hollie L. Baker
Registration No. 31,321
Attorney for Applicant

Wilmer Cutler Pickering
Hale and Dorr LLP
60 State Street
Boston, MA 02109
Telephone : (617) 526-6110
Facsimile: (617) 526-5000

APPOINTMENT OF AGENT

WHEREAS Jay N. Cohn (hereinafter "Dr. Cohn"), an individual whose principal address is 4848 Russell Avenue South, Minneapolis, Minnesota 55410, is the owner of U.S. Patent No. 4,868,179 entitled "Method of Reducing Mortality Associated with Congestive Heart Failure Using Hydralazine and Isosorbide Dinitrate" which was granted September 19, 1989;

WHEREAS NitroMed, Inc. (hereinafter "NitroMed"), a Delaware Corporation whose principal address is 125 Spring Street, Lexington, Massachusetts 02421, entered into a license agreement with Dr. Cohn under which NitroMed was granted certain rights under U.S. Patent No. 4,868,179;

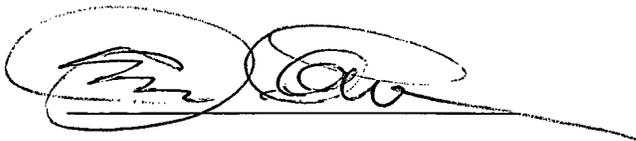
WHEREAS NitroMed is marketing a drug within the scope of the claims of U.S. Patent No. 4, 868,179, including BiDil[®] (isosorbide dinitrate/hydralazine hydrochloride);

WHEREAS NitroMed received marketing approval on June 23, 2005 from the United States Food and Drug Administration to market the fixed dose combination of isosorbide dinitrate and hydralazine hydrochloride under the mark BiDil[®];

WHEREAS 35 U.S.C. Section 156, known as the Drug Price Competition and Patent Term Restoration Act of 1984, provides at (a)(3) that an application for an extension of a patent term can be submitted by the owner of record of the patent or its agent;

NOW, THEREFORE, Dr. Cohn hereby appoints NitroMed, its subsidiaries and/or its designees as his agents for the express purpose of submitting the application for patent term extension for U.S. Patent No. 4, 868,179 covering BiDil[®] under 35 USC 156. This appointment shall be co-extensive with the term of the underlying license agreement.

DR. JAY N. COHN

A handwritten signature in black ink, appearing to read "J. Cohn", with a long horizontal flourish extending to the right.

Date: 8-5-05

POWER OF ATTORNEY

WHEREAS, NitroMed, Inc. (hereinafter "NitroMed"), having its principal place of business at 125 Spring Street, Lexington MA 02421, has entered into a license agreement with Jay N. Cohn (hereinafter "Dr. Cohn"), having a principal address at 4848 Russell Avenue South, Minneapolis, Minnesota 55410, and by virtue thereof has been granted certain rights under U.S. Patent No. 4, 868,179;

WHEREAS, NitroMed is marketing a drug within the scope of the claims of U.S. Patent No. 4,868,179 including a drug sold under the mark BiDil®;

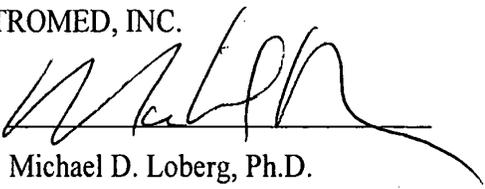
WHEREAS, NitroMed has received marketing approval on June 23, 2005 from the United States Food and Drug Administration to market the drug sold under the mark BiDil®;

WHEREAS, 35 U.S.C. Section 156, known as the Drug Price Competition and Patent Term Restoration Act of 1984, provides at (a)(3) that an application for an extension of a patent term can be submitted by the owner of record of the patent or its agent;

WHEREAS, by virtue of APPOINTMENT OF AGENT signed by Dr. Cohn and dated August 5, 2005, NitroMed is authorized to designate a person as a NitroMed agent for the express purpose of submitting an application for patent term extension of said U.S. Patent No. 4, 868,179.

NOW, THEREFORE, NitroMed hereby designates Hollie L. Baker (Reg. No. 31,321) who is a lawyer in the law firm of Wilmer Cutler Pickering Hale and Dorr LLP, 60 State Street, Boston MA 02109, and serves NitroMed in intellectual property matters, as an authorized attorney for submitting and prosecuting said application for patent term extension.

NITROMED, INC.

By: 

Michael D. Loberg, Ph.D.

Date: August 8, 2005

A

Bidi[®]

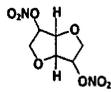
(isosorbide dinitrate and hydralazine hydrochloride)

Tablets

DESCRIPTION

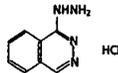
Bidi is a fixed-dose combination of isosorbide dinitrate, a vasodilator with effects on both arteries and veins, and hydralazine hydrochloride, a predominantly arterial vasodilator.

Isosorbide dinitrate is described chemically as 1,4:3,6-dihydro-D-glucitol-2,5-dinitrate and its structural formula is:



Isosorbide dinitrate is a white to off-white, crystalline powder with the empirical formula $C_{12}H_{16}N_2O_8$ and a molecular weight of 236.14. It is freely soluble in organic solvents such as alcohol, chloroform and ether, but is only sparingly soluble in water.

Hydralazine hydrochloride is described chemically as 1-hydrazinophthalazine monohydrochloride, and its structural formula is:



Hydralazine HCl is a white to off-white, crystalline powder with the empirical formula $C_{10}H_{10}N_4HCl$ and a molecular weight of 196.64. It is soluble in water, slightly soluble in alcohol, and very slightly soluble in ether.

Each Bidi Tablet for oral administration contains 20 mg of isosorbide dinitrate and 37.5 mg of hydralazine hydrochloride.

The inactive ingredients in Bidi tablets include: anhydrous lactose, microcrystalline cellulose, sodium starch glycolate, colloidal silicon dioxide, magnesium stearate, hydroxytoluene, FD&C Yellow No.6 aluminum lake, polyethylene glycol, titanium dioxide, polysorbate 80.

CLINICAL PHARMACOLOGY

Mechanism of Action

The mechanism of action underlying the beneficial effects of Bidi in the treatment of heart failure has not been established.

Isosorbide dinitrate is a vasodilator affecting both arteries and veins. Its diastolic properties result from the release of nitric oxide and the subsequent activation of guanylyl cyclase, and ultimate relaxation of vascular smooth muscle.

Several well-controlled clinical trials have used exercise testing to assess the anti-anginal efficacy of chronically delivered nitrates. In the large majority of these trials, active agents were no more effective than placebo after 24 hours (or less) of continuous therapy. Attempts to overcome nitrate tolerance by dose escalation, even to doses far in excess of those used acutely, have consistently failed. Only after nitrates have been absent from the body for several hours has response to nitrates been restored.

Hydralazine is a selective dilator of arterial smooth muscle. Animal data suggest that hydralazine may also mitigate tolerance to nitrates.

Pharmacokinetics

Hydralazine

Absorption and Distribution: About 2/3 of a 50-mg dose of ^{14}C -hydralazine HCl given in gelatin capsules was absorbed in hypertensive subjects. In patients with heart failure, mean absolute bioavailability of a single oral dose of hydralazine 75 mg varies from 10 to 26%, with the higher percentages in slow acetylators (See *Metabolism and Elimination*). Administration of doses escalating from 75 mg to 1000 mg led to congestive heart failure patients resulted in an up to 9-fold increase in the dose normalized AUC, indicating non-linear kinetics of hydralazine, probably reflecting saturable first pass metabolism.

After intravenous administration of hydralazine in a dose of 0.3 mg/kg, the steady-state volume of distribution in patients with congestive heart failure was 2.2 L/kg.

Metabolism and Elimination: Metabolism is the main route for the elimination of hydralazine. Negligible amounts of unchanged hydralazine are excreted in urine. Hydralazine is metabolized by acetylation, ring oxidation and conjugation with endogenous compounds including pyruvic acid. Acetylation occurs predominantly during the first pass after oral administration which explains the dependence of the absolute bioavailability on the acetylator phenotype. About 50% of patients are fast acetylators and have lower exposure.

After oral administration of hydralazine, the major circulating metabolites are hydralazine pyruvate hydrazine and methylhydrazinophthalazine. Hydralazine is the main pharmacologically active entity; hydralazine pyruvate hydrazine has only minimal hypotensive and tachycardic activity. The pharmacological activity of methylhydrazinophthalazine has not been determined. The major identified metabolite of hydralazine excreted in urine is acetylhydrazinophthalazine.

Isosorbide Dinitrate

Absorption and Distribution: Absorption of isosorbide dinitrate from tablets after oral dosing is nearly complete. The average bioavailability of isosorbide dinitrate is about 25%, but is highly variable (10%-90%) due to first-pass metabolism and increases progressively during chronic therapy. Serum concentrations reach their maximum about one hour after ingestion.

The volume of distribution of isosorbide dinitrate is 2 to 4 L/kg. About 28% of circulating isosorbide dinitrate is protein bound.

Under steady-state conditions, isosorbide dinitrate accumulates significantly in muscle (pedal) and vein (saphenous) well relative to simultaneous plasma concentrations.

Metabolism and Elimination: Isosorbide dinitrate undergoes extensive first-pass metabolism in the liver and is cleared at a rate of 2 to 4 L/minute with a serum half-life of about 1 hour. Isosorbide dinitrate's clearance is primarily by denitration to the 2-mononitrate (15 to 25%) and the 5-mononitrate (75 to 85%). Both metabolites have biological activity, especially the 5-mononitrate which has an overall half-life of about 5 hours. The 5-mononitrate is cleared by isosorbide glucuronidation to the 5-mononitrate glucuronides, and by denitration/hydrolysis to sorbitol. The 2-mononitrate

appears to participate in the same metabolic pathways with a half-life of about 2 hours.

Most isosorbide dinitrate is eliminated renally as conjugated metabolites.

Bidi

Absorption and Bioavailability: Following a single 75-mg oral dose of hydralazine plus 40 mg of isosorbide dinitrate to 19 healthy adults, peak plasma concentrations of hydralazine (88 ng/mL/65 kg) and isosorbide dinitrate (76 ng/mL/65 kg) were reached in 1 hour. The half-lives were about 4 hours for hydralazine and about 2 hours for isosorbide dinitrate. Peak plasma concentrations of the two active metabolites, isosorbide 2-mononitrate and isosorbide 5-mononitrate, were 86 and 364 ng/mL/65 kg, respectively, at about 2 hours. No information is currently available regarding the effect of food on the bioavailability of hydralazine or isosorbide dinitrate from Bidi tablets.

Special Populations

Pediatric: The pharmacokinetics of hydralazine and isosorbide dinitrate, alone or in combination, have not been determined in patients below the age of 18 years.

Geriatric: The pharmacokinetics of hydralazine and isosorbide dinitrate, alone or in combination, have not been determined in patients over 65 years of age.

Renal Impairment: The effect of renal impairment on the pharmacokinetics of hydralazine has not been determined. In a study with 49 hypertensive patients on chronic therapy with hydralazine in daily doses of 25-200 mg, the daily dose of hydralazine in 19 subjects with severely impaired renal function (creatinine clearance 5-28 mL/min) and in 17 subjects with normal renal function (creatinine clearance >100 mL/min) was not different, suggesting no need for dose adjustment in patients with renal impairment. The dialyzability of hydralazine has not been determined. In three studies, renal insufficiency did not affect the pharmacokinetics of isosorbide dinitrate. Dialysis is not an effective method for removing isosorbide dinitrate or its metabolite isosorbide 5-mononitrate from the body.

Hepatic Impairment: The effect of hepatic impairment on the pharmacokinetics of hydralazine alone has not been determined. Isosorbide dinitrate concentrations increase in patients with cirrhosis. There are no studies of hepatic impairment using Bidi.

Gender: There are no studies of gender-dependent effects with hydralazine. In a single dose study with isosorbide dinitrate, no gender-dependent differences in the pharmacokinetics of isosorbide dinitrate and its mononitrate metabolites were found.

No pharmacokinetic studies in special populations were conducted with Bidi.

Pharmacokinetic Drug-Drug Interactions

Hydralazine

Administration of hydralazine can increase the exposure to a number of drugs including beta blockers.

In healthy males administered a single oral dose of hydralazine 50 mg and propranolol 1 mg/kg, the C_{max} and AUC for propranolol increased by about 143% and 77%, respectively. In healthy subjects administered a single oral dose of hydralazine 50 mg and metoprolol 100 mg, the C_{max} and AUC for metoprolol increased by about 50% and 30%, respectively. In pre-emptive women, multiple doses of hydralazine 25 mg bid and metoprolol 50 mg bid increased the C_{max} and AUC for metoprolol by 88% and 38%, respectively.

In healthy males administered single oral doses of hydralazine 25 mg and either lisinopril 20 mg or enalapril 20 mg, C_{max} and AUC for lisinopril were each increased by about 30%, but enalapril concentrations were unaffected.

Intravenous co-administration of 0.2 mg/kg hydralazine HCl and 40 mg furosemide in Japanese patients with congestive heart failure resulted in a 21% increase in the clearance of furosemide.

Isosorbide Dinitrate

A single dose of 20 mg of isosorbide dinitrate was administered to healthy subjects after pretreatment with 80 mg propranolol for 48 hours, resulting in no impact on the pharmacokinetics of isosorbide dinitrate and isosorbide 5-mononitrate.

When single 100-mg oral doses of atenolol were administered 2 hours before isosorbide dinitrate at a 10-mg dose no differences in the pharmacokinetics of isosorbide dinitrate or its mononitrates were observed.

The vasodilating effects of coadministered isosorbide dinitrate may be additive to those of other vasodilators, especially alcohol when administered concomitantly with isosorbide dinitrate.

Bidi

No pharmacokinetic drug-drug interaction studies were conducted with Bidi.

Pharmacodynamics

The basis for the beneficial clinical effects of Bidi is not known. In a small study of patients with chronic heart failure administered single doses of hydralazine 75 mg, isosorbide dinitrate 20 mg, and the combination, the combination elicited a statistically significant decrease in pulmonary capillary wedge pressure compared to hydralazine alone. The increase in cardiac output, renal blood flow and limb blood flow with the combination, however, was not greater than with hydralazine alone. There is no study of hemodynamic effects following multiple dosing.

Clinical Trials

Bidi or a combination of isosorbide dinitrate and hydralazine hydrochloride was studied in two placebo-controlled clinical trials in 1,632 patients with mild to severe heart failure (mostly NYHA class II and III) and one active control trial (vs. enalapril) in 804 patients.

In the multicenter trial V-HEFT I, the combination of hydralazine and isosorbide dinitrate 75 mg/40 mg qd (n=188) was compared to placebo (n=273) in men with impaired cardiac function and reduced exercise tolerance (primarily NYHA class II and III), and on therapy with digitalis glycosides and diuretics. There was no overall significant difference in mortality between the two treatment groups. There was, however, a trend favoring hydralazine and isosorbide dinitrate, which on retrospective analysis, was attributable to an effect in blacks (n=128). Survival in white patients (n=324) was similar on placebo and the combination treatment.

In a second study of mortality, V-HEFT II, the combination of hydralazine and isosorbide dinitrate 75 mg/40 mg qd was compared to enalapril in 804 men with impaired cardiac function and reduced exercise tolerance (NYHA class I and II), and on therapy with digitalis glycosides and diuretics. The combination of hydralazine and isosorbide dinitrate was inferior to enalapril overall, but retrospective analysis showed that the difference was observed in the white population (n=574); there was essentially no difference in the black population (n=215).

Based on these retrospective analyses suggesting an effect on survival in black patients, but showing little evidence of an effect in the white population, a third study was conducted among black patients with heart failure.

The A-HEFT trial evaluated Bidi vs. placebo among 1,050 self-identified black patients

(over 95% NYHA class II) at 169 centers in the United States. All patients had stable symptomatic heart failure. Patients were required to have LVEF \leq 35% or left ventricular internal diastolic dimension > 2.9 cm/m² plus LVEF < 45%. Patients were maintained on stable background therapy and randomized to Bidi (n=518) or placebo (n=532). Bidi was initiated at 20 mg isosorbide dinitrate/37.5 mg hydralazine hydrochloride three times daily and titrated to a target dose of 40/75 mg three times daily or to the maximum tolerated dose. Patients were treated for up to 18 months.

The randomized population was 60% male, 1% NYHA class II, 95% NYHA class III and 4% NYHA class IV, with a mean age of 57 years, and was generally treated with standard treatments for heart failure including diuretics (94%, almost all loop diuretics), beta-blockers (87%), angiotensin converting enzyme inhibitors (ACE-I 78%), angiotensin II receptor blockers (ARBs 28%, either ACE-I or ARB (33%), digitalis glycosides (62%) and aldosterone antagonists (39%).

The primary end point was a composite score consisting of all-cause mortality, first hospitalization for heart failure, and responses to the Minnesota Living With Heart Failure questionnaire, with the individual components of the composite examined as separate endpoints. The trial was terminated early, at a mean follow-up of 12 months, primarily because of a statistically significant 43% reduction in all-cause mortality in the Bidi-treated group (p=0.012; see Table 1 and Figure 1). The primary endpoint was also statistically in favor of Bidi (p \leq 0.021). The Bidi-treated group also showed a 39% reduction in the risk of a first hospitalization for heart failure (p<0.001; see Table 1 and Figure 2) and had statistically significant improvement in response to the Minnesota Living With Heart Failure questionnaire, a self-report of the patient's functional status, at most time points (see Figure 3). Patients in both treatment groups had mean baseline questionnaire scores of 51 (out of a possible 100).

Table 1. Results of A-HEFT (Intent-to-Treat Population)

End point	Bidi [®] N=518	Placebo N=532	Hazard Ratio (95% CI)	Risk Reduction with Bidi	P-value
Composite score	-0.16±1.83	-0.47±2.04	N/A	N/A	≤0.021
All cause mortality	6.2%	10.2%	0.57 (0.37, 0.89)	43%	0.012
First hospitalization for heart failure	16.4%	24.4%	0.61 (0.46, 0.80)	39%	<0.001

Figure 1: Kaplan-Meier Plot of Time to Death by All Cause in Black Patients (A-HEFT)

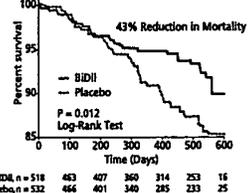


Figure 2: Kaplan-Meier Plot of Time to First Hospitalization for Heart Failure in Black Patients (A-HEFT)

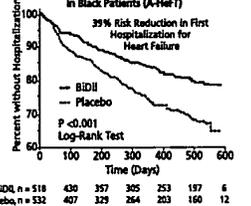
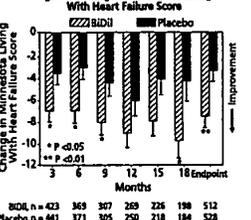
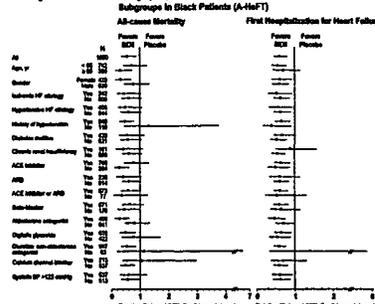


Figure 3: Change in Minnesota Living With Heart Failure Score (EZ2) Bidi vs Placebo



Effects on survival and hospitalizations for heart failure were similar in subgroups by age, gender, baseline disease, and use of concomitant medications, as shown in Figure 4.

Figure 4: Results for Demographic, Baseline Medication and Clinical Characteristics Subgroups in Black Patients (A-HEFT)



Bidi[®]
(isosorbide dinitrate and hydralazine hydrochloride)
Tablets

PC4928
Rev 06/05

Patients treated with BIDIL in the A-HeFT study had randomly measured blood pressures on average 3/3 mmHg lower than did patients on placebo. The contribution of the difference in blood pressure to the overall outcome difference is unknown. Whether both hydralazine and isosorbide dinitrate contribute to the overall outcome difference has not been studied in outcome trials. Isosorbide dinitrate and hydralazine have not been systematically studied for the treatment of heart failure as separate agents, and neither drug is indicated for heart failure.

INDICATIONS AND USAGE

BIDIL is indicated for the treatment of heart failure as an adjunct to standard therapy in self-identified black patients to improve survival, to prolong time to hospitalization for heart failure, and to improve patient-reported functional status. There is little experience in patients with NYHA class IV heart failure. Most patients in the clinical trial supporting effectiveness (A-HeFT) received a loop diuretic, an angiotensin converting enzyme inhibitor or an angiotensin II receptor blocker, and a beta blocker, and many also received a cardiac glycoside or an aldosterone antagonist.

CONTRAINDICATIONS

BIDIL is contraindicated in patients who are allergic to organic nitrates.

WARNINGS

Augmentation of the vasodilatory effects of isosorbide dinitrate by phosphodiesterase inhibitors such as sildenafil, vardenafil, or tadalafil could result in severe hypotension. The time course and dose dependence of this interaction have not been studied. Reasonable supportive care should consist of those measures used to treat a nitrate overdose with elevation of the extremities and central volume expansion.

PRECAUTIONS

General

The precautions that need to be taken when using BIDIL are those appropriate to each of its components.

Treatment with hydralazine hydrochloride may produce a clinical picture simulating systemic lupus erythematosus including glomerulonephritis.

If systemic lupus erythematosus-like symptoms occur in patients treated with BIDIL, discontinuation of BIDIL should be considered only after a thorough benefit-to-risk assessment. Symptoms and signs of systemic lupus erythematosus usually regress when hydralazine hydrochloride is discontinued but rashes have been detected many years later. Long-term treatment with steroids may be necessary. (See PRECAUTIONS, Laboratory Tests.)

Symptomatic hypotension, particularly with upright posture, may occur with even small doses of BIDIL. Therefore, BIDIL should be used with caution in patients who may be volume depleted or who, for whatever reason, are already hypotensive.

Hydralazine hydrochloride can cause tachycardia potentially leading to myocardial ischemia and anginal attacks.

Careful clinical and hemodynamic monitoring is recommended when BIDIL is administered to patients with acute myocardial infarction to avoid the hazards of hypertension and tachycardia.

Hydralazine hydrochloride has been associated with peripheral neuritis, evidenced by paresthesia, numbness, and tingling, which may be related to an antipyrindoxine effect. Pyridoxine should be added to BIDIL therapy if such symptoms develop.

Isosorbide dinitrate therapy may aggravate angina associated with hypertrophic cardiomyopathy.

Information for Patients

Patients should be informed of possible side effects and advised to take the medication regularly and continuously as directed.

Patients should be told that headaches often accompany treatment with BIDIL, especially during initiation of treatment. Headaches tend to subside even with continued dosing. Patients should be instructed to consult a physician to adjust the dose of BIDIL if headache continues with repeated dosing. Treatment of emerging headache was managed with acetaminophen in some clinical trial patients.

Treatment with BIDIL may be associated with lightheadedness on standing, especially after rising from a recumbent or seated position.

Patients should be cautioned that inadequate fluid intake or excessive fluid loss from perspiration, diarrhea or vomiting may lead to an excessive fall in blood pressure and cause lightheadedness or even syncope. If syncope does occur, BIDIL should be discontinued, and the prescribing physician should be notified as soon as possible.

Patients should be cautioned about the increased risk of hypotension especially if they are taking antihypertensive drugs concomitantly.

Patients should be cautioned against concomitant use of BIDIL with phosphodiesterase-5 inhibitor drugs used for the treatment of erectile dysfunction or pulmonary hypertension such as sildenafil citrate (Viagra®), Revatio™), vardenafil (Levitra®) or tadalafil (Cialis®). Use of BIDIL may produce an extreme drop in blood pressure that may result in fainting or may provoke chest pain or a heart attack.

Laboratory Tests

If symptoms suggestive of systemic lupus erythematosus occur, such as arthralgia, fever, chest pain, prolonged malaise, or other unexplained signs or symptoms, complete blood counts and antinuclear antibody titer determinations should be performed. A positive antinuclear antibody titer requires that the physician carefully weigh the benefits and risks of continued therapy with BIDIL.

Drug/Drug Interactions

Due to the hydralazine component of BIDIL, monoamine-oxidase inhibitors should be used with caution in patients receiving BIDIL.

Patients treated with BIDIL who receive any potent peripheral antihypertensive agent should be continuously observed for several hours for excessive fall in blood pressure.

The effects of BIDIL on vasodilators including alcohol may be additive.

Sildenafil: See WARNINGS.

Vardenafil: See WARNINGS.

Tadalafil: See WARNINGS.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Hydralazine Hydrochloride

An increased incidence of lung tumors (adenomas and adenocarcinomas) was observed in a lifetime study in Swiss albino mice given hydralazine hydrochloride continuously in their drinking water at a dosage of about 250 mg/kg per day (6 times the MHD provided by BIDIL on a body surface area basis). In a 2-year carcinogenicity study of rats given hydralazine hydrochloride by gavage at dose levels of 15, 30, and 60 mg/kg/day (up to 3 times the MHD of BIDIL on a body surface area basis), microscopic examination of the liver revealed a small, but statistically

significant increase in benign neoplastic nodules in males (high-dosage) and females (both high and intermediate dosage groups). Benign interstitial cell tumors of the testes were also significantly increased in the high-dose group.

Hydralazine hydrochloride is mutagenic in bacterial systems, and is positive in rat and rabbit hepatocyte DNA repair studies *in vitro*. Additional *in vivo* and *in vitro* studies using lymphoma cells, germinal cells, fibroblasts from mice, bone marrow cells from Chinese hamsters and fibroblasts from human cell lines did not demonstrate any mutagenic or clastogenic potential for hydralazine hydrochloride.

Isosorbide Dinitrate

No long-term animal studies have been performed to evaluate the mutagenic or carcinogenic potential of isosorbide dinitrate. A modified two-litter reproduction study among rats fed isosorbide dinitrate at 25 or 100 mg/kg/day (up to 9 times the Maximum Recommended Human Dose of BIDIL on a body surface area basis) revealed no evidence of altered fertility or gestation.

Pregnancy Category C

Isosorbide dinitrate has been shown to cause a dose-related increase in embryotoxicity (excess mummified pups) in rabbits at 70 mg/kg (12 times the MHD of BIDIL on a body surface area basis). Hydralazine hydrochloride is teratogenic in mice at 66 mg/kg and possibly in rabbits at 33 mg/kg (2 and 3 times the MHD of BIDIL on a body surface area basis). There are no animal studies assessing the teratogenicity of BIDIL.

A meta-analysis of randomized controlled trials comparing hydralazine hydrochloride with other antihypertensive agents for severe hypertension in pregnancy found that hydralazine hydrochloride was associated with significantly more maternal hypotension, placental abruption, caesarean sections and oliguria, with more adverse effects on fetal heart rate and with lower Apgar scores.

A combination of propranolol and hydralazine hydrochloride was administered to 13 patients with long-standing hypertension during 15 pregnancies. These pregnancies resulted in 14 live births and one unexplained stillbirth. The only neonatal complications were two cases of mild hypoglycemia. Hydralazine hydrochloride and its metabolites have been detected using a non-selective assay in maternal and umbilical plasma in patients treated with the drug during pregnancy.

Isosorbide dinitrate has been used for effective acute and sub-chronic control of hypertension in pregnant women, but there are no studies using it in a chronic regimen and assessing its effects on pregnant women and/or the fetus.

There are no studies using BIDIL in pregnant women. Therefore, BIDIL should be used with caution during pregnancy and only if the potential benefit justifies the potential risk to the fetus.

Nursing mothers

The possible excretion of hydralazine in breast milk has not been determined. It is also not known whether isosorbide dinitrate is excreted in human milk. No studies have been performed with BIDIL. Caution should be exercised when BIDIL is administered to a nursing woman.

Pediatric use

The safety and effectiveness of BIDIL in children have not been established.

Geriatric use

Clinical studies of BIDIL did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in response between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic and renal function, and of concomitant disease or other drug therapies.

Isosorbide dinitrate, its active metabolites, and hydralazine may be eliminated more slowly in elderly patients.

ADVERSE REACTIONS

BIDIL

BIDIL has been evaluated for safety in 517 heart failure patients in A-HeFT. A total of 317 of these patients received BIDIL for at least 6 months, and 220 received BIDIL for at least 12 months. In A-HeFT, 21% of the patients discontinued BIDIL for adverse experiences compared to 12% who discontinued placebo. Overall, adverse events were more common in BIDIL-treated than in placebo-treated patients. Table 2 lists adverse events reported with an incidence of $\geq 2\%$ in patients treated with BIDIL in A-HeFT, and, after rounding to the nearest 1%, occurring more frequently than in the placebo group, regardless of causality. Headache and dizziness were the two most frequent adverse events and were more than twice as frequent in the BIDIL group. The most common reasons for discontinuing BIDIL in the A-HeFT trial were headache (7%) and dizziness (4%).

Table 2. Adverse Events Occurring in the A-HeFT Study in $\geq 2\%$ of Patients Treated with BIDIL.

	BIDIL (N=517) (% of patients)	Placebo (N=527) (% of patients)
Headache	50	21
Dizziness	32	14
Chest pain	16	15
Asthenia	14	11
Nausea	10	6
Bronchitis	8	7
Hypotension	8	4
Sinusitis	4	2
Ventricular tachycardia	4	2
Palpitations	4	3
Hyperglycemia	4	3
Rhinitis	4	3
Paresthesia	4	2
Vomiting	4	2
Amblyopia	3	1
Hyperlipidemia	3	2
Tachycardia	2	1

The following adverse events were reported in A-HeFT in at least 1% but less than 2% of patients treated with BIDIL, and also occurred in at least 0.5% more patients than in placebo-treated patients; all such events are included unless they are too non-specific to be meaningful or appear to reflect underlying disease.

Body as a Whole: Allergic reaction, malaise.

Central nervous system: Somnolence.

Gastrointestinal: Cholecystitis.

Metabolic: Hypercholesterolemia.

Musculoskeletal: Arthralgia, myalgia, tendon disorder.

Skin: Alopecia, angioedema, swelling.

In the V-HeFT I and II studies, a total of 587 patients with heart failure were treated with the combination of isosorbide dinitrate and hydralazine hydrochloride. The type, pattern, frequency and severity of adverse experiences reported in these studies were similar to those reported in A-HeFT, and no unusual adverse experiences were reported.

Prior experience with BIDIL components

The following additional adverse events have been reported with hydralazine hydrochloride or isosorbide dinitrate but not necessarily with BIDIL:

Digestive: paralytic ileus.

Cardiovascular: paradoxical pressor response, crescendo angina.

Neurologic: peripheral neuritis, numbness, tingling, muscle cramps, psychotic reactions, disorientation.

Genitourinary: difficulty in urination.

Hematologic: blood dyscrasias, agranulocytosis, purpura, splenomegaly.

Hypersensitive Reactions: eosinophilia, hepatitis.

Other: nasal congestion, flushing, lacrimation, conjunctivitis.

OVERDOSAGE

There are no documented cases of overdose with BIDIL. The signs and symptoms of overdose with BIDIL are expected to be those of excessive pharmacologic effect and those that may occur with overdose of either isosorbide dinitrate or hydralazine hydrochloride administered alone.

Acute toxicity: No deaths due to acute poisoning have been reported.

Signs and Symptoms: The signs and symptoms of overdose with BIDIL are expected to be those of excessive pharmacologic effect, i.e., vasodilatation, reduced cardiac output and hypotension, and signs and symptoms include headache, confusion, tachycardia and generalized skin flushing. Complications can include myocardial ischemia and subsequent myocardial infarction, cardiac arrhythmia, and profound shock. Syncope, coma and death may ensue without appropriate treatment.

Treatment: There is no specific antidote.

Support of the cardiovascular system is of primary importance. Shock should be treated with plasma expanders, vasopressors, and positive inotropic agents. The gastric contents should be evacuated, taking adequate precautions to prevent aspiration. These manipulations have to be carried out after cardiovascular status has been stabilized, since they might precipitate cardiac arrhythmias or increase the depth of shock.

In patients with renal disease or congestive heart failure, therapy resulting in central volume expansion is not without hazard. Treatment of isosorbide dinitrate overdose in these patients may be difficult, and invasive monitoring may be required.

No data are available to suggest physiological maneuvers (e.g., maneuvers to change the pH of the urine) that might accelerate elimination of the components of BIDIL. Dialysis is not effective in removing circulating isosorbide dinitrate. The dialyzability of hydralazine has not been determined.

Methemoglobinemia

Nitrate ions liberated during metabolism of isosorbide dinitrate can oxidize hemoglobin into methemoglobin.

There are case reports of significant methemoglobinemia in association with moderate overdoses of organic nitrates.

Methemoglobin levels are measurable by most clinical laboratories. Methemoglobinemia could be serious in chronic heart failure patients because of already compromised vascular bed-tissue gas exchange dynamics. Classically, methemoglobinemic blood is described as chocolate brown, without color change on exposure to air.

When methemoglobinemia is diagnosed, the treatment of choice is methylene blue, 1 to 2 mg/kg intravenously.

DOSSAGE AND ADMINISTRATION

Treatment with BIDIL should be initiated at a dose of one BIDIL Tablet, 3 times a day. BIDIL may be titrated to a maximum tolerated dose, not to exceed two BIDIL Tablets, 3 times a day.

There is no adequate experience in heart failure with doses of BIDIL other than those recommended and no experience with use of individual components.

Although titration of BIDIL can be rapid (3-5 days), some patients may experience side effects and may take longer to reach their maximum tolerated dose. The dosage may be decreased to as little as one-half BIDIL Tablet 3 times a day if intolerable side effects occur. Efforts should be made to titrate up as soon as side effects subside.

HOW SUPPLIED

BIDIL Tablets contain 20 mg of isosorbide dinitrate plus 37.5 mg of hydralazine hydrochloride. They are biconvex, approximately 8 mm in diameter, scored, film-coated, orange tablets debossed "20" on one side over the score and "H" on the other side.

NDC 12948-001-12 bottle of 180.

Keep bottles tightly closed.

Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature.]

Protect from light. Dispense in a light-resistant, tight container.

Rx only

Manufactured by:
NitroMed, Inc.
125 Spring Street
Lexington, MA 02421 USA

by

Schwarz Pharma Mfg., Inc.
P.O. Box 328
1101 C Avenue W
Seymour, IN 47274 USA

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NDA 20-727

NitroMed, Inc.
Attention: Michael Sabolinski, M.D.
Senior VP, Clinical Development & Regulatory Affairs
125 Spring Street
Lexington, MA 02421

Dear Dr. Sabolinski:

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

We acknowledge receipt of your submissions dated December 21, 2004 and January 4, 7, and 19, March 22, April 11, 15, 22, 25, 26, 27, and 29, May 6 and 9, and June 9, 10, and 23, 2005.

Your submission of December 21, 2004 constituted a complete response to our July 2, 1997 not approvable letter.

This new drug application provides for the use of BiDil® (isosorbide dinitrate and hydralazine hydrochloride) Tablets, 20 mg/37.5 mg for the treatment of heart failure as an adjunct to standard therapy in self-identified black patients to improve survival, to prolong time to hospitalization for heart failure, and to improve patient-reported functional status.

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

The final printed labeling (FPL) must be identical in content to the enclosed labeling (text for the package insert) and the immediate container labels submitted on June 9, 2005. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "FPL for approved NDA 20-727." Approval of this submission by FDA is not required before the labeling is used.

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 refer you to our May 25, 2005 letter waiving the pediatric study requirement for this application.

Please continue to monitor the (b) (4)----- as an impurity/degradant in the release and stability testing of BiDil[®] tablets with a release/shelf life limit of not more than (NMT) (b) (4). 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.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

The following dissolution method and specification for both isosorbide dinitrate and hydralazine hydrochloride are recommended:

- 1) USP Apparatus I at (b) (4)PM in (b) (4)l of (b) (4)N HCl
- 2) Specification not less than (b) (4)h 30 minutes

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Cardio-Renal Drug Products and two copies of both the promotional materials and the package insert directly to:

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

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

If you have any questions, please call:

Dianne Paroan
Regulatory Project Manager
(301) 594-5308

Sincerely,

{See appended electronic signature page}

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

Enclosure

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

/s/

Robert Temple

6/23/05 05:16:51 PM

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HYDRALAZINE HYDROCHLORIDE N008303 001 TABLET, COATED NOVARTIS PHARMACEUTICALS CORP APRESOLINE	ORAL	59 RT 10, EAST HANOVER, NJ, 079361080, UNITED STATES RX APPEF 13-MAR-1952 25MG
HYDRALAZINE HYDROCHLORIDE N008303 002 TABLET, COATED NOVARTIS PHARMACEUTICALS CORP APRESOLINE	ORAL	59 RT 10, EAST HANOVER, NJ, 079361080, UNITED STATES RX APPEF 13-MAR-1952 50MG
HYDRALAZINE HYDROCHLORIDE N008303 003 INJECTION NOVARTIS PHARMACEUTICALS CORP APRESOLINE	IM - IV	59 RT 10, EAST HANOVER, NJ, 079361080, UNITED STATES RX APPEF 13-MAR-1952 DISCN 21-OCT-1998 20MG/ML
HYDRALAZINE HYDROCHLORIDE N008303 004 TABLET, COATED NOVARTIS PHARMACEUTICALS CORP APRESOLINE	ORAL	59 RT 10, EAST HANOVER, NJ, 079361080, UNITED STATES RX APPEF 04-AUG-1952 10MG
HYDRALAZINE HYDROCHLORIDE N008303 005 TABLET, COATED NOVARTIS PHARMACEUTICALS CORP APRESOLINE	ORAL	59 RT 10, EAST HANOVER, NJ, 079361080, UNITED STATES RX APPEF 15-JAN-1953 100MG
HYDRALAZINE HYDROCHLORIDE N009296 001 TABLET, COATED NOVARTIS PHARMACEUTICALS CORP SERPASIL-APRESOLINE	ORAL	59 RT 10, EAST HANOVER, NJ, 079361080, UNITED STATES RX APPEF 01-APR-1954 DISCN 21-SEP-1959 0.2MG 50MG
RESERFINE HYDRALAZINE HYDROCHLORIDE N009296 002 TABLET, COATED NOVARTIS PHARMACEUTICALS CORP SERPASIL-APRESOLINE	ORAL	59 RT 10, EAST HANOVER, NJ, 079361080, UNITED STATES RX APPEF 01-APR-1954 DISCN 31-DEC-1991 WDLAG 04-SEP-1996 0.2MG 50MG
RESERFINE HYDRALAZINE HYDROCHLORIDE N009296 003 TABLET, COATED NOVARTIS PHARMACEUTICALS CORP SERPASIL-APRESOLINE	ORAL	59 RT 10, EAST HANOVER, NJ, 079361080, UNITED STATES RX APPEF 29-DEC-1954 DISCN 21-SEP-1959 0.1MG 25MG
RESERFINE HYDRALAZINE HYDROCHLORIDE N009296 004 TABLET, COATED NOVARTIS PHARMACEUTICALS CORP SERPASIL-APRESOLINE	ORAL	59 RT 10, EAST HANOVER, NJ, 079361080, UNITED STATES RX APPEF 01-APR-1954 DISCN 31-DEC-1991 WDLAG 04-SEP-1996 0.1MG 25MG
RESERFINE HYDRALAZINE HYDROCHLORIDE N012026 001 TABLET, COATED NOVARTIS PHARMACEUTICALS CORP APRESOLINE-ESIDRIX	ORAL	59 RT 10, EAST HANOVER, NJ, 079361080, UNITED STATES RX APPEF 15-OCT-1959 DISCN 29-MAR-1961 WDLAG 29-SEP-1995 15MG 25MG
HYDROCHLOROTHIAZIDE HYDRALAZINE HYDROCHLORIDE N012026 002 TABLET, COATED NOVARTIS PHARMACEUTICALS CORP APRESOLINE-ESIDRIX	ORAL	59 RT 10, EAST HANOVER, NJ, 079361080, UNITED STATES RX APPEF 29-MAR-1961 DISCN 25-JAN-1995 WDLAG 29-SEP-1995

IVAX PHARMACEUTICALS INC HYDRALAZINE HCL AND HYDROCHLOROTHIAZIDE	140 LEGRAND AVE, NORTHVALE, NJ, 07647, UNITED STATES	
HYDROCHLOROTHIAZIDE	APPEF 10-SEP-1975 DISCN 27-NOV-1979 WDLAG 05-JAN-1998	
HYDRALAZINE HYDROCHLORIDE	15MG	
N083877 001 TABLET	25MG	
IVAX PHARMACEUTICALS INC		
HYDROSERPINE PLUS (R-H-H)	140 LEGRAND AVE, NORTHVALE, NJ, 07647, UNITED STATES	
RESERPINE	APPEF 18-SEP-1975 DISCN 09-SEP-1997 WDLAG 05-JAN-1998	
HYDROCHLOROTHIAZIDE	0.1MG	
HYDRALAZINE HYDROCHLORIDE	15MG	
N084106 001 TABLET, FILM COATED	25MG	
MUTUAL PHARMACEUTICAL CO INC		
HYDRALAZINE HCL	1100 ORTHODOX ST, PHILADELPHIA, PA, 19124, UNITED STATES	
HYDRALAZINE HYDROCHLORIDE	APPEF 05-AUG-1974 DISCN 15-JUL-1977	
N084106 002 TABLET, FILM COATED	25MG	
MUTUAL PHARMACEUTICAL CO INC		
HYDRALAZINE HCL	1100 ORTHODOX ST, PHILADELPHIA, PA, 19124, UNITED STATES	
HYDRALAZINE HYDROCHLORIDE	APPEF 15-JUL-1977 DISCN 12-SEP-1996	
N084107 001 TABLET, FILM COATED	25MG	
MUTUAL PHARMACEUTICAL CO INC		
HYDRALAZINE HCL	1100 ORTHODOX ST, PHILADELPHIA, PA, 19124, UNITED STATES	
HYDRALAZINE HYDROCHLORIDE	APPEF 08-NOV-1974 DISCN 10-AUG-1977	
N084107 002 TABLET, FILM COATED	50MG	
MUTUAL PHARMACEUTICAL CO INC		
HYDRALAZINE HCL	1100 ORTHODOX ST, PHILADELPHIA, PA, 19124, UNITED STATES	
HYDRALAZINE HYDROCHLORIDE	APPEF 10-AUG-1977 DISCN 12-SEP-1996	
N084291 001 TABLET	50MG	
IVAX PHARMACEUTICALS INC		
HYDRALAZINE HCL, HYDROCHLOROTHIAZIDE AND RESERPINE	140 LEGRAND AVE, NORTHVALE, NJ, 07647, UNITED STATES	
RESERPINE	APPEF 03-FEB-1975 DISCN 09-SEP-1997 WDLAG 05-JAN-1998	
HYDROCHLOROTHIAZIDE	0.1MG	
HYDRALAZINE HYDROCHLORIDE	15MG	
N084301 001 TABLET	25MG	
TEVA PHARMACEUTICALS USA INC		
DRALZINE	650 CATHILL RD, BOX 904, SELLEYSVILLE, PA, 18960, UNITED STATES	
HYDRALAZINE HYDROCHLORIDE	APPEF 15-OCT-1975 DISCN 05-APR-1995 WDLAG 21-AUG-1995	
N084437 001 TABLET	25MG	
IVAX PHARMACEUTICALS INC		
HYDRALAZINE HCL	140 LEGRAND AVE, NORTHVALE, NJ, 07647, UNITED STATES	
HYDRALAZINE HYDROCHLORIDE	APPEF 19-FEB-1976 DISCN 09-SEP-1997 WDLAG 05-JAN-1998	
N084443 001 TABLET	25MG	
IVAX PHARMACEUTICALS INC		
HYDRALAZINE HCL	140 LEGRAND AVE, NORTHVALE, NJ, 07647, UNITED STATES	
HYDRALAZINE HYDROCHLORIDE	APPEF 08-SEP-1975 DISCN 09-SEP-1997 WDLAG 05-JAN-1998	
N084469 001 TABLET	10MG	
IVAX PHARMACEUTICALS INC		
HYDRALAZINE HCL	140 LEGRAND AVE, NORTHVALE, NJ, 07647, UNITED STATES	
HYDRALAZINE HYDROCHLORIDE	APPEF 19-FEB-1976 DISCN 23-JUL-1976 WDLAG 05-JAN-1998	
N084469 002 TABLET	50MG	
IVAX PHARMACEUTICALS INC		
HYDRALAZINE HCL	140 LEGRAND AVE, NORTHVALE, NJ, 07647, UNITED STATES	

HYDRALAZINE HCL					
N084503 001 TABLET, FILM COATED	HYDRALAZINE HYDROCHLORIDE				
WATSON LABORATORIES INC					
HYDRALAZINE HCL					
N084504 001 TABLET, FILM COATED	HYDRALAZINE HYDROCHLORIDE				
WATSON LABORATORIES INC					
HYDRALAZINE HCL					
N084581 001 TABLET	HYDRALAZINE HYDROCHLORIDE				
IVAX PHARMACEUTICALS INC					
HYDRALAZINE HCL					
N084617 001 TABLET	HYDRALAZINE HYDROCHLORIDE				
ECN LABORATORIES MANUFACTURING INC					
DRALSERP					
RESERPINE					
N084735 001 CAPSULE	HYDRALAZINE HYDROCHLORIDE				
NOVARTIS PHARMACEUTICALS CORP					
APRESAZIDE					
N084810 001 CAPSULE	HYDROCHLOROTHIAZIDE				
NOVARTIS PHARMACEUTICALS CORP	HYDRALAZINE HYDROCHLORIDE				
APRESAZIDE					
N084811 001 CAPSULE	HYDROCHLOROTHIAZIDE				
NOVARTIS PHARMACEUTICALS CORP	HYDRALAZINE HYDROCHLORIDE				
APRESAZIDE					
N084876 001 TABLET	HYDROCHLOROTHIAZIDE				
ECN LABORATORIES MANUFACTURING INC	HYDRALAZINE HYDROCHLORIDE				
HYDRAP-ES					
RESERPINE					
N084897 001 TABLET	HYDROCHLOROTHIAZIDE				
ABC HOLDING CORP	HYDRALAZINE HYDROCHLORIDE				
CAM-AP-ES					
RESERPINE					
N084922 001 TABLET	HYDROCHLOROTHIAZIDE				
IMPAX LABORATORIES INC	HYDRALAZINE HYDROCHLORIDE				
HYDRALAZINE HCL					
HYDRALAZINE HYDROCHLORIDE					
RX	APPEF 23-JUL-1976	DISCN 09-SEP-1997	WDLAG 05-JAN-1998		
ORAL	50MG				
RX	311 BONNIE CIR, BOX 1900, CORONA, CA, 928801900, UNITED STATES				
ORAL	APPEF 23-NOV-1976				
50MG					
RX	311 BONNIE CIR, BOX 1900, CORONA, CA, 928801900, UNITED STATES				
ORAL	APPEF 23-NOV-1976				
25MG					
RX	140 LEGRAND AVE, NORTHVALE, NJ, 07647, UNITED STATES				
ORAL	APPEF 12-SEP-1975	DISCN 09-SEP-1997	WDLAG 05-JAN-1998		
100MG					
RX	227 15 NORTH CONDUIT AVE, LAURELTON, NY, 11413, UNITED STATES				
ORAL	APPEF 13-AUG-1976	DISCN 12-FEB-1992			
0.1MG					
25MG					
RX	59 RT 10, EAST HANOVER, NJ, 079361080, UNITED STATES				
ORAL	APPEF 26-MAY-1976				
25MG					
25MG					
RX	59 RT 10, EAST HANOVER, NJ, 079361080, UNITED STATES				
ORAL	APPEF 26-MAY-1976				
50MG					
50MG					
RX	59 RT 10, EAST HANOVER, NJ, 079361080, UNITED STATES				
ORAL	APPEF 26-MAY-1976				
50MG					
100MG					
RX	227 15 NORTH CONDUIT AVE, LAURELTON, NY, 11413, UNITED STATES				
ORAL	APPEF 10-SEP-1981	DISCN 12-FEB-1992			
0.1MG					
15MG					
25MG					
RX	70945 VAN DYKE AVE, BOX 307, ROMEO, MI, 48065, UNITED STATES				
ORAL	APPEF 20-NOV-1979	DISCN 08-JAN-2002			
0.1MG					
15MG					
25MG					
RX	30831 HUNTWOOD AVE, HAYWARD, CA, 94544, UNITED STATES				
ORAL	APPEF 21-SEP-1976	DISCN 02-OCT-2000	WDLAG 17-SEP-2001		
25MG					

N084923 001 TABLET IMPAX LABORATORIES INC HYDRALAZINE HCL	ORAL	30831 HUNTWOOD AVE, HAYWARD, CA, 94544, UNITED STATES RX APPEF 03-AUG-1976 DISCN 22-JUN-2000 50MG
HYDRALAZINE HYDROCHLORIDE N084956 001 TABLET EON LABORATORIES MANUFACTURING INC HYDRALAZINE HCL	ORAL	227 15 NORTH CONDUIT AVE, LAURELTON, NY, 11413, UNITED STATES RX APPEF 27-OCT-1976 DISCN 01-JUN-1978 25MG
HYDRALAZINE HYDROCHLORIDE N085088 001 TABLET EON LABORATORIES MANUFACTURING INC HYDRALAZINE HCL	ORAL	227 15 NORTH CONDUIT AVE, LAURELTON, NY, 11413, UNITED STATES RX APPEF 18-AUG-1976 DISCN 12-FEB-1992 50MG
HYDRALAZINE HYDROCHLORIDE N085352 001 TABLET WATSON LABORATORIES INC HYDRALAZINE HCL	ORAL	33 RALPH AVE, BOX 30, COPIAGUE, NY, 117260030, UNITED STATES RX APPEF 10-FEB-1977 DISCN 09-FEB-1984 25MG
HYDRALAZINE HYDROCHLORIDE N085358 001 TABLET, FILM COATED WATSON LABORATORIES INC HYDRALAZINE HCL	ORAL	33 RALPH AVE, BOX 30, COPIAGUE, NY, 117260030, UNITED STATES RX APPEF 10-FEB-1977 DISCN 09-FEB-1984 50MG
HYDRALAZINE HYDROCHLORIDE N085373 001 TABLET WATSON LABORATORIES INC HYDROCHLOROTHIAZIDE W/ HYDRALAZINE	ORAL	33 RALPH AVE, BOX 30, COPIAGUE, NY, 117260030, UNITED STATES RX APPEF 14-FEB-1977 15MG 25MG WDLAG 07-OCT-1991
HYDROCHLOROTHIAZIDE HYDRALAZINE HYDROCHLORIDE N085440 001 CAPSULE WATSON LABORATORIES INC HYDRALAZINE HCL AND HYDROCHLOROTHIAZIDE	ORAL	33 RALPH AVE, BOX 30, COPIAGUE, NY, 117260030, UNITED STATES RX APPEF 04-MAR-1982 50MG 100MG WDLAG 07-OCT-1991
HYDROCHLOROTHIAZIDE HYDRALAZINE HYDROCHLORIDE N085446 001 CAPSULE WATSON LABORATORIES INC HYDRALAZINE HCL AND HYDROCHLOROTHIAZIDE	ORAL	33 RALPH AVE, BOX 30, COPIAGUE, NY, 117260030, UNITED STATES RX APPEF 04-MAR-1982 50MG 50MG WDLAG 07-OCT-1991
HYDROCHLOROTHIAZIDE HYDRALAZINE HYDROCHLORIDE N085457 001 CAPSULE WATSON LABORATORIES INC HYDRALAZINE HCL AND HYDROCHLOROTHIAZIDE	ORAL	33 RALPH AVE, BOX 30, COPIAGUE, NY, 117260030, UNITED STATES RX APPEF 04-MAR-1982 25MG 25MG WDLAG 07-OCT-1991
HYDROCHLOROTHIAZIDE HYDRALAZINE HYDROCHLORIDE N085532 001 TABLET WATSON LABORATORIES INC HYDRALAZINE HCL	ORAL	311 BONNIE CIR, CORONA, CA, 928781900, UNITED STATES RX APPEF 14-APR-1977 DISCN 24-MAY-1982 25MG
HYDRALAZINE HYDROCHLORIDE N085532 002 TABLET WATSON LABORATORIES INC HYDRALAZINE HCL	ORAL	311 BONNIE CIR, CORONA, CA, 928781900, UNITED STATES RX APPEF 24-MAY-1982 25MG WDLAG 28-MAY-1991
HYDRALAZINE HYDROCHLORIDE N085533 001 TABLET WATSON LABORATORIES INC	ORAL	311 BONNIE CIR, CORONA, CA, 928781900, UNITED STATES

HYDRALAZINE HCL					
HYDRALAZINE HYDROCHLORIDE					
N085533 002 TABLET	ORAL	APPEF 14-APR-1977	DISCN 24-MAY-1982		
WATSON LABORATORIES INC		50MG			
HYDRALAZINE HCL					
HYDRALAZINE HYDROCHLORIDE					
N085549 001 TABLET	ORAL	APPEF 25-MAY-1982	DISCN 01-MAY-2001	WDLAG 28-MAY-1991	
WATSON LABORATORIES INC		50MG			
RESERPINE, HYDRALAZINE HCL AND HYDROCHLOROTHIAZIDE					
RESERPINE					
HYDROCHLOROTHIAZIDE					
HYDRALAZINE HYDROCHLORIDE					
N085771 001 TABLET	ORAL	APPEF 29-SEP-1977	DISCN 01-MAY-2001		
WATSON LABORATORIES INC		0.1MG			
HYDRALAZINE, HYDROCHLOROTHIAZIDE W/ RESERPINE		15MG			
RESERPINE		25MG			
HYDROCHLOROTHIAZIDE					
HYDRALAZINE HYDROCHLORIDE					
N085827 001 TABLET	ORAL	APPEF 21-APR-1978			
WATSON LABORATORIES INC		0.1MG			
HYDRALAZINE AND HYDROCHLOROTHIAZIDE		15MG			
HYDROCHLOROTHIAZIDE		25MG			
HYDRALAZINE HYDROCHLORIDE					
N085893 001 TABLET	ORAL	APPEF 21-OCT-1977		WDLAG 08-APR-1991	
SOLVAY PHARMACEUTICALS		15MG			
UNIPRES		25MG			
RESERPINE					
HYDROCHLOROTHIAZIDE					
HYDRALAZINE HYDROCHLORIDE					
N086088 001 TABLET	ORAL	APPEF 10-FEB-1978	DISCN 20-MAR-1990	WDLAG 23-SEP-1999	
VITARINE PHARMACEUTICALS INC		0.1MG			
HYDRALAZINE HCL		15MG			
HYDRALAZINE HYDROCHLORIDE		25MG			
N086242 002 TABLET	ORAL	APPEF 23-OCT-1978	DISCN 02-MAY-1985		
CLONMEL HEALTHCARE LTD		25MG			
HYDRALAZINE HCL					
HYDRALAZINE HYDROCHLORIDE					
N086243 001 TABLET	ORAL	APPEF 23-OCT-1978	DISCN 22-MAY-2003		
CLONMEL HEALTHCARE LTD		50MG			
HYDRALAZINE HCL					
HYDRALAZINE HYDROCHLORIDE					
N086298 001 TABLET	ORAL	APPEF 23-OCT-1978	DISCN 22-MAY-2003		
SOLVAY PHARMACEUTICALS		25MG			
UNIPRES					
RESERPINE					
HYDROCHLOROTHIAZIDE					
HYDRALAZINE HYDROCHLORIDE					
N086961 001 TABLET	ORAL	APPEF 27-MAR-1978	DISCN 18-SEP-1997	WDLAG 29-DEC-1997	
PAR PHARMACEUTICAL INC		0.1MG			
HYDRALAZINE HCL		15MG			
		25MG			
12 INDUSTRIAL AVE, UPPER SADDLE RIVER, NJ, 07458, UNITED STATES					
RX					
APPEF 27-FEB-1980		DISCN 26-JUL-1983			

HYDRALAZINE HYDROCHLORIDE N086961 002 TABLET PAR PHARMACEUTICAL INC HYDRALAZINE HCL	ORAL	25MG	12 INDUSTRIAL AVE, UPPER SADDLE RIVER, NJ, 07458, UNITED STATES RX APPEF 27-FEB-1980
HYDRALAZINE HYDROCHLORIDE N086962 001 TABLET PAR PHARMACEUTICAL INC HYDRALAZINE HCL	ORAL	25MG	12 INDUSTRIAL AVE, UPPER SADDLE RIVER, NJ, 07458, UNITED STATES RX APPEF 27-FEB-1980
HYDRALAZINE HYDROCHLORIDE N087085 001 TABLET MYLAN PHARMACEUTICALS INC	ORAL	50MG	781 CHESTNUT RIDGE RD, BOX 4310, MORGANTOWN, WV, 265054310, UNITED STATES RX APPEF 29-MAY-1981 DISCN 29-APR-1987 WDLAG 26-MAY-1995
HYDRALAZINE HCL-HYDROCHLOROTHIAZIDE-RESERPINE RESERPINE HYDROCHLOROTHIAZIDE HYDRALAZINE HYDROCHLORIDE N087210 001 TABLET SOLVAY PHARMACEUTICALS SER-A-GEN	ORAL	0.1MG 15MG 25MG	25 5TH ST NORTHWEST, ATLANTA, GA, 30308, UNITED STATES RX APPEF 08-FEB-1980 DISCN 0.1MG WDLAG 23-MAY-1994 0.1MG 15MG 25MG
RESERPINE HYDROCHLOROTHIAZIDE HYDRALAZINE HYDROCHLORIDE N087213 001 CAPSULE SOLVAY PHARMACEUTICALS HYDRALAZINE HCL AND HYDROCHLOROTHIAZIDE	ORAL	50MG 50MG	901 SAWYER RD, MARIETTA, GA, 30062, UNITED STATES RX APPEF 08-FEB-1982 DISCN 04-AUG-1999 WDLAG 23-SEP-1999
HYDRALAZINE HYDROCHLORIDE N087556 001 TABLET WATSON LABORATORIES INC RESERPINE, HYDRALAZINE HCL AND HYDROCHLOROTHIAZIDE	ORAL	0.1MG 15MG 25MG	311 BONNIE CIR, BOX 1900, CORONA, CA, 928801900, UNITED STATES RX APPEF 06-AUG-1981 DISCN 16-MAY-1994 WDLAG 11-AUG-1994
RESERPINE HYDROCHLOROTHIAZIDE HYDRALAZINE HYDROCHLORIDE N087608 001 CAPSULE SOLVAY PHARMACEUTICALS HYDRALAZINE HCL AND HYDROCHLOROTHIAZIDE	ORAL	0.1MG 15MG 25MG	901 SAWYER RD, MARIETTA, GA, 30062, UNITED STATES RX APPEF 08-FEB-1982 DISCN 04-AUG-1999 WDLAG 23-SEP-1999
HYDROCHLOROTHIAZIDE HYDRALAZINE HYDROCHLORIDE N087609 001 CAPSULE SOLVAY PHARMACEUTICALS HYDRALAZINE HCL AND HYDROCHLOROTHIAZIDE	ORAL	25MG 25MG	25 5TH ST NORTHWEST, ATLANTA, GA, 30308, UNITED STATES RX APPEF 08-FEB-1982 DISCN 21-MAY-1992 WDLAG 02-MAY-1994
HYDROCHLOROTHIAZIDE HYDRALAZINE HYDROCHLORIDE N087709 001 TABLET LEDERLE LABORATORIES DIV AMERICAN CYANAMID CO	ORAL	50MG 100MG	401 NORTH MIDDLETOWN RD, PEARL RIVER, NY, 109651299, UNITED STATES RX APPEF 13-MAY-1982
RESERPINE, HYDROCHLOROTHIAZIDE, AND HYDRALAZINE HC RESERPINE HYDROCHLOROTHIAZIDE HYDRALAZINE HYDROCHLORIDE N087712 001 TABLET VANGARD LABORATORIES INC DIV MIDWAY MEDICAL CO	ORAL	0.1MG 15MG 25MG	103 SAMSON ST, GLASGOW, KY, 42141, UNITED STATES

HYDRALAZINE HCL	RX	APPEF 08-DEC-1981	DISCN 21-JUL-1992	
HYDRALAZINE HYDROCHLORIDE		25MG		
N087751 001 TABLET	ORAL			
USL PHARMA INC				301 SOUTH CHEROKEE ST, DENVER, CO, 80223, UNITED STATES
HYDRALAZINE HCL	RX	APPEF 29-MAR-1982	WDLAG 28-JAN-1991	
HYDRALAZINE HYDROCHLORIDE		50MG		
N087780 001 TABLET	ORAL			
USL PHARMA INC				301 SOUTH CHEROKEE ST, DENVER, CO, 80223, UNITED STATES
HYDRALAZINE HCL	RX	APPEF 29-MAR-1982	WDLAG 28-JAN-1991	
HYDRALAZINE HYDROCHLORIDE		25MG		
N087836 001 TABLET	ORAL			
PAR PHARMACEUTICAL INC				12 INDUSTRIAL AVE, UPPER SADDLE RIVER, NJ, 07458, UNITED STATES
HYDRALAZINE HCL	RX	APPEF 05-OCT-1982		
HYDRALAZINE HYDROCHLORIDE		10MG		
N087908 001 TABLET	ORAL			
VANGARD LABORATORIES INC DIV MIDWAY MEDICAL CO				103 SAMSON ST, GLASGOW, KY, 42141, UNITED STATES
HYDRALAZINE HCL	RX	APPEF 07-MAY-1982	DISCN 23-MAR-1989	WDLAG 13-MAR-1991
HYDRALAZINE HYDROCHLORIDE		50MG		
N088177 001 TABLET	ORAL			
PUREPAC PHARMACEUTICAL CO DIV PUREPAC INC				200 ELMORA AVE, ELIZABETH, NJ, 07207, UNITED STATES
HYDRALAZINE HCL	RX	APPEF 29-JUL-1983	DISCN 12-AUG-1997	WDLAG 29-DEC-1997
HYDRALAZINE HYDROCHLORIDE		25MG		
N088178 001 TABLET	ORAL			
PUREPAC PHARMACEUTICAL CO DIV PUREPAC INC				200 ELMORA AVE, ELIZABETH, NJ, 07207, UNITED STATES
HYDRALAZINE HCL	RX	APPEF 15-AUG-1983	WDLAG 25-SEP-1997	
HYDRALAZINE HYDROCHLORIDE		50MG		
N088240 001 TABLET	ORAL			
WEST WARD PHARMACEUTICAL CORP				465 INDUSTRIAL WAY WEST, EATONTOWN, NJ, 07724, UNITED STATES
HYDRALAZINE HCL	RX	APPEF 27-MAY-1983	DISCN 17-DEC-1985	
HYDRALAZINE HYDROCHLORIDE		25MG		
N088241 001 TABLET	ORAL			
WEST WARD PHARMACEUTICAL CORP				465 INDUSTRIAL WAY WEST, EATONTOWN, NJ, 07724, UNITED STATES
HYDRALAZINE HCL	RX	APPEF 27-MAY-1983	DISCN 17-DEC-1985	
HYDRALAZINE HYDROCHLORIDE		50MG		
N088310 001 TABLET	ORAL			
ASCOT HOSP PHARMACEUTICALS INC DIV TRAVENOL LABORA				7701 NORTH AUSTIN AVE, SKOKIE, IL, 60077, UNITED STATES
HYDRALAZINE HCL	RX	APPEF 19-DEC-1984	DISCN 06-MAR-1987	
HYDRALAZINE HYDROCHLORIDE		25MG		
N088311 001 TABLET	ORAL			
ASCOT HOSP PHARMACEUTICALS INC DIV TRAVENOL LABORA				7701 NORTH AUSTIN AVE, SKOKIE, IL, 60077, UNITED STATES
HYDRALAZINE HCL	RX	APPEF 19-DEC-1984	DISCN 06-MAR-1987	
HYDRALAZINE HYDROCHLORIDE		50MG		
N088356 001 CAPSULE	ORAL			
IVAX PHARMACEUTICALS INC				140 LEGRAND AVE, NORTHVALE, NJ, 07647, UNITED STATES
HYDRALAZINE HCL W/ HYDROCHLOROTHIAZIDE 25/25	RX	APPEF 10-APR-1984	DISCN 09-SEP-1997	WDLAG 05-JAN-1998
HYDROCHLOROTHIAZIDE		25MG		
HYDRALAZINE HYDROCHLORIDE		25MG		
N088357 001 CAPSULE	ORAL			
IVAX PHARMACEUTICALS INC				140 LEGRAND AVE, NORTHVALE, NJ, 07647, UNITED STATES

HYDRALAZINE HCL W/ HYDROCHLOROTHIAZIDE 50/50	RX	APPEF 10-APR-1984	DISCN 09-SEP-1997	WDLAG 05-JAN-1998
HYDROCHLOROTHIAZIDE		50MG		
HYDRALAZINE HYDROCHLORIDE		50MG		
N088358 001 CAPSULE	ORAL			
IVAX PHARMACEUTICALS INC				
HYDRALAZINE HCL W/ HYDROCHLOROTHIAZIDE 100/50	RX	140 LEGRAND AVE, NORTHVALE, NJ, 07647, UNITED STATES		
HYDROCHLOROTHIAZIDE		APPEF 10-APR-1984	DISCN 18-DEC-1990	WDLAG 05-JAN-1998
HYDRALAZINE HYDROCHLORIDE		50MG		
N088376 001 TABLET	ORAL	25 5TH ST NORTHWEST, ATLANTA, GA, 30308, UNITED STATES		
SOLVAY PHARMACEUTICALS		APPEF 28-OCT-1983	DISCN 04-AUG-1999	WDLAG 23-SEP-1999
RESERPINE, HYDRALAZINE HCL AND HYDROCHLOROTHIAZIDE	RX	0.1MG		
RESERPINE		15MG		
HYDROCHLOROTHIAZIDE		25MG		
HYDRALAZINE HYDROCHLORIDE				
N088391 001 TABLET	ORAL	12 INDUSTRIAL AVE, UPPER SADDLE RIVER, NJ, 07458, UNITED STATES		
PAR PHARMACEUTICAL INC		RX		
HYDRALAZINE HCL		APPEF 27-SEP-1983		
HYDRALAZINE HYDROCHLORIDE		100MG		
N088467 001 TABLET	ORAL	72 EAGLE ROCK AVE, BOX 371, EAST HANOVER, NJ, 07936, UNITED STATES		
PLIVA INC		RX		
HYDRALAZINE HCL		APPEF 01-MAY-1984		
HYDRALAZINE HYDROCHLORIDE		25MG		
N088468 001 TABLET	ORAL	72 EAGLE ROCK AVE, BOX 371, EAST HANOVER, NJ, 07936, UNITED STATES		
PLIVA INC		RX		
HYDRALAZINE HCL		APPEF 01-MAY-1984		
HYDRALAZINE HYDROCHLORIDE		50MG		
N088517 001 INJECTION	IM - IV	1845 TONNE RD, ELK GROVE VILLAGE, IL, 60007, UNITED STATES		
SOLOPAK LABORATORIES INC		RX		
HYDRALAZINE HCL		APPEF 22-AUG-1985		WDLAG 21-JUL-1999
HYDRALAZINE HYDROCHLORIDE		20MG/ML		
N088518 001 INJECTION	IM - IV	1845 TONNE RD, ELK GROVE VILLAGE, IL, 60007, UNITED STATES		
SMITH AND NEPHEW SOLOPAK DIV SMITH AND NEPHEW		RX		
HYDRALAZINE HCL		APPEF 20-APR-1984	DISCN 28-MAY-1991	
HYDRALAZINE HYDROCHLORIDE		20MG/ML		
N088560 001 TABLET	ORAL	101 EAST MAIN STREET, LITTLE FALLS, NJ, 07424, UNITED STATES		
AMIDE PHARMACEUTICAL INC		RX		
HYDRALAZINE HCL		APPEF 04-OCT-1984	DISCN 01-SEP-1994	WDLAG 18-NOV-1994
HYDRALAZINE HYDROCHLORIDE		25MG		
N088570 001 TABLET	ORAL	1100 ORTHODOX ST, PHILADELPHIA, PA, 19124, UNITED STATES		
MUTUAL PHARMACEUTICAL CO INC		RX		
RESERPINE, HYDRALAZINE HCL AND HYDROCHLOROTHIAZIDE	RX	APPEF 10-APR-1984	DISCN 12-SEP-1996	
RESERPINE		0.1MG		
HYDROCHLOROTHIAZIDE		15MG		
HYDRALAZINE HYDROCHLORIDE		25MG		
N088649 001 TABLET	ORAL	101 EAST MAIN STREET, LITTLE FALLS, NJ, 07424, UNITED STATES		
AMIDE PHARMACEUTICAL INC		RX		
HYDRALAZINE HCL		APPEF 18-OCT-1984	DISCN 01-SEP-1994	WDLAG 18-NOV-1994
HYDRALAZINE HYDROCHLORIDE		50MG		

N088652 001 TABLET QUANTUM PHARMICS LTD HYDRALAZINE HCL	ORAL	10 EAST, AMITYVILLE, NY, 11701, UNITED STATES RX APPEF 08-MAY-1984 50MG
HYDRALAZINE HYDROCHLORIDE N088657 001 TABLET QUANTUM PHARMICS LTD HYDRALAZINE HCL	ORAL	10 EAST, AMITYVILLE, NY, 11701, UNITED STATES RX APPEF 15-JUN-1984 25MG WDLAG 05-DEC-1990
HYDRALAZINE HYDROCHLORIDE N088671 001 TABLET QUANTUM PHARMICS LTD HYDRALAZINE HCL	ORAL	10 EAST, AMITYVILLE, NY, 11701, UNITED STATES RX APPEF 01-MAY-1984 10MG WDLAG 05-DEC-1990
HYDRALAZINE HYDROCHLORIDE N088686 001 TABLET QUANTUM PHARMICS LTD HYDRALAZINE HCL	ORAL	10 EAST, AMITYVILLE, NY, 11701, UNITED STATES RX APPEF 01-MAY-1984 100MG WDLAG 05-DEC-1990
HYDRALAZINE HYDROCHLORIDE N088728 001 TABLET MUTUAL PHARMACEUTICAL CO INC HYDRALAZINE HCL	ORAL	1100 ORTHODOX ST, PHILADELPHIA, PA, 19124, UNITED STATES RX APPEF 11-APR-1985 DISCN 12-SEP-1996 10MG
HYDRALAZINE HYDROCHLORIDE N088729 001 TABLET MUTUAL PHARMACEUTICAL CO INC HYDRALAZINE HCL	ORAL	1100 ORTHODOX ST, PHILADELPHIA, PA, 19124, UNITED STATES RX APPEF 11-APR-1985 DISCN 12-SEP-1996 100MG
HYDRALAZINE HYDROCHLORIDE N088787 001 TABLET SUPERPHARM CORP HYDRALAZINE HCL	ORAL	155 OVAL DR, CENTRAL ISLIP, NY, 11722, UNITED STATES RX APPEF 28-AUG-1984 DISCN 23-APR-1990 WDLAG 28-JAN-1991 10MG
HYDRALAZINE HYDROCHLORIDE N088788 001 TABLET SUPERPHARM CORP HYDRALAZINE HCL	ORAL	155 OVAL DR, CENTRAL ISLIP, NY, 11722, UNITED STATES RX APPEF 28-AUG-1984 DISCN 23-APR-1990 WDLAG 28-JAN-1991 25MG
HYDRALAZINE HYDROCHLORIDE N088789 001 TABLET SUPERPHARM CORP HYDRALAZINE HCL	ORAL	155 OVAL DR, CENTRAL ISLIP, NY, 11722, UNITED STATES RX APPEF 28-AUG-1984 DISCN 23-APR-1990 WDLAG 28-JAN-1991 50MG
HYDRALAZINE HYDROCHLORIDE N088846 001 TABLET ABC HOLDING CORP HYDRALAZINE HCL	ORAL	70945 VAN DYKE AVE, BOX 307, ROMEO, MI, 48065, UNITED STATES RX APPEF 26-FEB-1985 10MG
HYDRALAZINE HYDROCHLORIDE N088847 001 TABLET ABC HOLDING CORP HYDRALAZINE HCL	ORAL	70945 VAN DYKE AVE, BOX 307, ROMEO, MI, 48065, UNITED STATES RX APPEF 26-FEB-1985 25MG
HYDRALAZINE HYDROCHLORIDE N088848 001 TABLET ABC HOLDING CORP HYDRALAZINE HCL	ORAL	70945 VAN DYKE AVE, BOX 307, ROMEO, MI, 48065, UNITED STATES RX APPEF 26-FEB-1985 50MG
HYDRALAZINE HYDROCHLORIDE N088849 001 TABLET	ORAL	

ABC HOLDING CORP HYDRALAZINE HCL	ORAL	70945 VAN DYKE AVE, BOX 307, ROMEO, MI, 48065, UNITED STATES RX APPEF 26-FEB-1985 100MG
HYDRALAZINE HYDROCHLORIDE N088946 001 CAPSULE PAR PHARMACEUTICAL INC HYDRA-ZIDE	ORAL	12 INDUSTRIAL AVE, UPPER SADDLE RIVER, NJ, 07458, UNITED STATES RX APPEF 21-OCT-1985 50MG 50MG
HYDROCHLOROTHIAZIDE HYDRALAZINE HYDROCHLORIDE N088957 001 CAPSULE PAR PHARMACEUTICAL INC HYDRA-ZIDE	ORAL	12 INDUSTRIAL AVE, UPPER SADDLE RIVER, NJ, 07458, UNITED STATES RX APPEF 21-OCT-1985 25MG 25MG
HYDROCHLOROTHIAZIDE HYDRALAZINE HYDROCHLORIDE N088961 001 CAPSULE PAR PHARMACEUTICAL INC HYDRA-ZIDE	ORAL	12 INDUSTRIAL AVE, UPPER SADDLE RIVER, NJ, 07458, UNITED STATES RX APPEF 21-OCT-1985 50MG 100MG
HYDROCHLOROTHIAZIDE HYDRALAZINE HYDROCHLORIDE N089097 001 TABLET PLIVA INC	ORAL	72 EAGLE ROCK AVE, BOX 371, EAST HANOVER, NJ, 07936, UNITED STATES RX APPEF 18-DEC-1985 10MG
HYDRALAZINE HCL HYDRALAZINE HYDROCHLORIDE N089098 001 TABLET PLIVA INC	ORAL	1827 PACIFIC ST, BROOKLYN, NY, 1123333599, UNITED STATES RX APPEF 15-JAN-1986 25MG
HYDRALAZINE HYDROCHLORIDE N089178 001 TABLET HALSEY DRUG CO INC HYDRALAZINE HCL	ORAL	1827 PACIFIC ST, BROOKLYN, NY, 1123333599, UNITED STATES RX APPEF 15-JAN-1986 100MG
HYDRALAZINE HYDROCHLORIDE N089200 001 CAPSULE SUPERPHARM CORP HYDRALAZINE HCL AND HYDROCHLOROTHIAZIDE	ORAL	155 OVAL DR, CENTRAL ISLIP, NY, 11722, UNITED STATES RX APPEF 09-FEB-1987 DISCN 23-APR-1990 WDLAG 28-JAN-1991 25MG 25MG
HYDROCHLOROTHIAZIDE HYDRALAZINE HYDROCHLORIDE N089201 001 CAPSULE SUPERPHARM CORP HYDRALAZINE HCL AND HYDROCHLOROTHIAZIDE	ORAL	155 OVAL DR, CENTRAL ISLIP, NY, 11722, UNITED STATES RX APPEF 09-FEB-1987 DISCN 01-DEC-2003 50MG 50MG
HYDROCHLOROTHIAZIDE HYDRALAZINE HYDROCHLORIDE N089218 001 TABLET HALSEY DRUG CO INC HYDRALAZINE HCL	ORAL	1827 PACIFIC ST, BROOKLYN, NY, 1123333599, UNITED STATES RX APPEF 22-JAN-1986 10MG WDLAG 14-MAR-1996
HYDRALAZINE HYDROCHLORIDE		

N089222 001 TABLET HALSEY DRUG CO INC HYDRALAZINE HCL	ORAL	1827 PACIFIC ST, BROOKLYN, NY, 112333599, UNITED STATES RX	APPEF 22-JAN-1986 DISCN 02-JUN-1995 WDLAG 21-AUG-1995 50MG
HYDRALAZINE HYDROCHLORIDE N089258 001 TABLET MUTUAL PHARMACEUTICAL CO INC HYDRALAZINE HCL	ORAL	1100 ORTHODOX ST, PHILADELPHIA, PA, 19124, UNITED STATES RX	APPEF 05-MAY-1986 25MG
HYDRALAZINE HYDROCHLORIDE N089259 001 TABLET MUTUAL PHARMACEUTICAL CO INC HYDRALAZINE HCL	ORAL	1100 ORTHODOX ST, PHILADELPHIA, PA, 19124, UNITED STATES RX	APPEF 05-MAY-1986 50MG
HYDRALAZINE HYDROCHLORIDE N089359 001 TABLET MUTUAL PHARMACEUTICAL CO INC HYDRALAZINE HCL	ORAL	1100 ORTHODOX ST, PHILADELPHIA, PA, 19124, UNITED STATES RX	APPEF 25-JUL-1986 10MG
HYDRALAZINE HYDROCHLORIDE N089532 001 INJECTION AMERICAN PHARMACEUTICAL PARTNERS INC HYDRALAZINE HCL	IM - IV	2045 NORTH CORNELL AVE, MELROSE PARK, IL, 60160, UNITED STATES RX	APPEF 11-AUG-1987 DISCN 06-MAR-1992 20MG/ML
HYDRALAZINE HYDROCHLORIDE			

ISOSORBIDE DINITRATE N012093 001 TABLET BIOVAIL LABORATORIES INC	ORAL	1001 G ST NORTHWEST STE 500 WEST, WASHINGTON, DC, 20001, UNITED STATES RX	APPEF 29-JUL-1988 40MG	
ISORDIL ISOSORBIDE DINITRATE N012093 002 TABLET BIOVAIL LABORATORIES INC	ORAL	1001 G ST NORTHWEST STE 500 WEST, WASHINGTON, DC, 20001, UNITED STATES RX	APPEF 29-JUL-1988 10MG	
ISORDIL ISOSORBIDE DINITRATE N012093 003 TABLET BIOVAIL LABORATORIES INC	ORAL	1001 G ST NORTHWEST STE 500 WEST, WASHINGTON, DC, 20001, UNITED STATES RX	APPEF 29-JUL-1988 10MG	
ISORDIL W/ PHENOBARBITAL PHENOBARBITAL ISOSORBIDE DINITRATE N012093 005 TABLET BIOVAIL LABORATORIES INC	ORAL	1001 G ST NORTHWEST STE 500 WEST, WASHINGTON, DC, 20001, UNITED STATES RX	APPEF 03-MAY-1961 15MG 10MG	WDLEF 02-FEB-1984
ISORDIL ISOSORBIDE DINITRATE N012093 006 TABLET BIOVAIL LABORATORIES INC	ORAL	1001 G ST NORTHWEST STE 500 WEST, WASHINGTON, DC, 20001, UNITED STATES RX	APPEF 29-JUL-1988 30MG	
ISORDIL ISOSORBIDE DINITRATE N012093 007 TABLET BIOVAIL LABORATORIES INC	ORAL	1001 G ST NORTHWEST STE 500 WEST, WASHINGTON, DC, 20001, UNITED STATES RX	APPEF 29-JUL-1988 20MG	
ISORDIL ISOSORBIDE DINITRATE N012882 001 TABLET, SUSTAINED ACTION WYETH AYERST LABORATORIES ISORDIL	ORAL	BOX 8299, PHILADELPHIA, PA, 191018299, UNITED STATES RX	APPEF 29-JUL-1988 5MG	
ISORDIL ISOSORBIDE DINITRATE N012882 002 CAPSULE, SUSTAINED ACTION WYETH AYERST LABORATORIES ISORDIL	ORAL	BOX 8299, PHILADELPHIA, PA, 191018299, UNITED STATES RX	APPEF 29-JUL-1988 40MG	DISCN 26-JUN-2000 WDLAG 17-SEP-2003
ISORDIL ISOSORBIDE DINITRATE N012940 001 TABLET BIOVAIL LABORATORIES INC	ORAL	1001 G ST NORTHWEST STE 500 WEST, WASHINGTON, DC, 20001, UNITED STATES RX	APPEF 29-JUL-1988 40MG	DISCN 18-AUG-1998 WDLAG 17-SEP-2003
ISORDIL ISOSORBIDE DINITRATE N012940 003 TABLET BIOVAIL LABORATORIES INC	SUBLINGUAL	1001 G ST NORTHWEST STE 500 WEST, WASHINGTON, DC, 20001, UNITED STATES RX	APPEF 20-DEC-1961 5MG	DISCN 29-JAN-1968
ISORDIL ISOSORBIDE DINITRATE N012940 003 TABLET BIOVAIL LABORATORIES INC	SUBLINGUAL	1001 G ST NORTHWEST STE 500 WEST, WASHINGTON, DC, 20001, UNITED STATES RX	APPEF 29-JUL-1988 5MG	

N012940 004 TABLET BIOVAIL LABORATORIES INC ISORDIL	SUBLINGUAL 1001 G ST NORTHWEST STE 500 WEST, WASHINGTON, DC, 20001, UNITED STATES RX	APPEF 29-JUL-1988 2.5MG	1001 G ST NORTHWEST STE 500 WEST, WASHINGTON, DC, 20001, UNITED STATES
N012940 005 TABLET BIOVAIL LABORATORIES INC ISORBIDE DINITRATE	SUBLINGUAL 1001 G ST NORTHWEST STE 500 WEST, WASHINGTON, DC, 20001, UNITED STATES RX	APPEF 29-JUL-1988 10MG	1001 G ST NORTHWEST STE 500 WEST, WASHINGTON, DC, 20001, UNITED STATES
N016191 001 TABLET ASTRAZENECA PHARMACEUTICALS LP SORBITRATE	SUBLINGUAL 1800 CONCORD PIKE, WILMINGTON, DE, 19850, UNITED STATES RX	APPEF 01-APR-1996 5MG	DISCN 30-JUL-1998 WDLAG 25-SEP-1998
N016191 002 TABLET ASTRAZENECA PHARMACEUTICALS LP SORBITRATE	SUBLINGUAL 1800 CONCORD PIKE, WILMINGTON, DE, 19850, UNITED STATES RX	APPEF 01-APR-1996 2.5MG	DISCN 30-JUL-1998 WDLAG 25-SEP-1998
N016192 001 TABLET ASTRAZENECA PHARMACEUTICALS LP SORBITRATE	ORAL 1800 CONCORD PIKE, BOX 8355, WILMINGTON, DE, 198038355, UNITED STATES RX	APPEF 01-APR-1996 5MG	DISCN 04-OCT-2002 WDLAG 17-SEP-2003
N016192 002 TABLET ASTRAZENECA PHARMACEUTICALS LP SORBITRATE	ORAL 1800 CONCORD PIKE, BOX 8355, WILMINGTON, DE, 198038355, UNITED STATES RX	APPEF 01-APR-1996 10MG	DISCN 04-OCT-2002 WDLAG 17-SEP-2003
N016193 001 TABLET ICI AMERICAS INC SORBITRATE W/ PHENOBARBITAL	ORAL NEW MURPHY RD AND CONCORD PIKE, WILMINGTON, DE, 19897, UNITED STATES RX	APPEF 16-JAN-1968 15MG 10MG	WDLAP 04-FEB-1980
N016776 002 TABLET (IMMED./COMP. RELEASE), ASTRAZENECA PHARMACEUTICALS LP SORBITRATE	ORAL 1800 CONCORD PIKE, BOX 8355, WILMINGTON, DE, 198038355, UNITED STATES RX	APPEF 01-APR-1996 5MG	DISCN 02-OCT-2002
N016776 003 TABLET (IMMED./COMP. RELEASE), ASTRAZENECA PHARMACEUTICALS LP SORBITRATE	ORAL 1800 CONCORD PIKE, BOX 8355, WILMINGTON, DE, 198038355, UNITED STATES RX	APPEF 01-APR-1996 10MG	DISCN 02-OCT-2002
N016776 004 TABLET (IMMED./COMP. RELEASE), SORBITRATE	ORAL 1800 CONCORD PIKE, BOX 8355, WILMINGTON, DE, 198038355, UNITED STATES RX	APPEF 01-APR-1996 10MG	DISCN 02-OCT-2002

ASTRAZENECA PHARMACEUTICALS LP		1800 CONCORD PIKE, BOX 8355, WILMINGTON, DE, 198038355, UNITED STATES	
SORBITRATE		RX	APPEF 21-JAN-1982 DISCN 03-AUG-1984 WDLAG 17-SEP-2003 5MG
ISOSORBIDE DINITRATE	ORAL	BOX 751, WILMINGTON, DE, 19897, UNITED STATES	
N017226 001 TABLET, SUSTAINED ACTION		RX	APPEF 30-APR-1985 WDLFF 07-AUG-2000 40MG
ZENECA PHARMACEUTICALS DIV ZENECA INC		BOX 2038, MILWAUKEE, WI, 53201, UNITED STATES	
SORBITRATE SA SRT		RX	APPEF 02-SEP-1988
ISOSORBIDE DINITRATE	ORAL	BOX 3038, MILWAUKEE, WI, 53201, UNITED STATES	
N01790 001 CAPSULE, SUSTAINED ACTION		RX	APPEF 02-SEP-1988 40MG
SCHWARZ PHARMA INC		909 3RD AVE, NEW YORK, NY, 100224731, UNITED STATES	
DILATRATE-SR		RX	APPEF 30-DEC-1998 40MG
ISOSORBIDE DINITRATE	ORAL	1100 ORTHODOX ST, PHILADELPHIA, PA, 19124, UNITED STATES	
N040009 001 TABLET, SUSTAINED ACTION		RX	APPEF 18-SEP-1986 DISCN 12-SEP-1996 2.5MG
INWOOD LABORATORIES INC SUB FOREST LABORATORIES IN		311 BONNIE CIR, BOX 1900, CORONA, CA, 928801900, UNITED STATES	
ISOSORBIDE DINITRATE		RX	APPEF 29-SEP-1987 5MG
ISOSORBIDE DINITRATE	SUBLINGUAL	311 BONNIE CIR, BOX 1900, CORONA, CA, 928801900, UNITED STATES	
N084204 001 TABLET		RX	APPEF 07-JAN-1988 10MG
MUTUAL PHARMACEUTICAL CO INC		311 BONNIE CIR, BOX 1900, CORONA, CA, 928801900, UNITED STATES	
ISOSORBIDE DINITRATE		RX	APPEF 26-FEB-1988 2.5MG
ISOSORBIDE DINITRATE	SUBLINGUAL	311 BONNIE CIR, BOX 1900, CORONA, CA, 928801900, UNITED STATES	
N086031 001 TABLET		RX	APPEF 06-JAN-1988 5MG
WATSON LABORATORIES INC		465 INDUSTRIAL WAY WEST, EATONTOWN, NJ, 07724, UNITED STATES	
ISOSORBIDE DINITRATE		RX	APPEF 29-OCT-1987 2.5MG
ISOSORBIDE DINITRATE	ORAL	465 INDUSTRIAL WAY WEST, EATONTOWN, NJ, 07724, UNITED STATES	
N086032 001 TABLET		RX	APPEF 02-NOV-1987 5MG
WATSON LABORATORIES INC		465 INDUSTRIAL WAY WEST, EATONTOWN, NJ, 07724, UNITED STATES	
ISOSORBIDE DINITRATE		RX	APPEF 29-OCT-1987 10MG
ISOSORBIDE DINITRATE	SUBLINGUAL	311 BONNIE CIR, BOX 1900, CORONA, CA, 928801900, UNITED STATES	
N086033 001 TABLET		RX	APPEF 06-JAN-1988 5MG
WATSON LABORATORIES INC		465 INDUSTRIAL WAY WEST, EATONTOWN, NJ, 07724, UNITED STATES	
ISOSORBIDE DINITRATE		RX	APPEF 29-OCT-1987 2.5MG
ISOSORBIDE DINITRATE	ORAL	465 INDUSTRIAL WAY WEST, EATONTOWN, NJ, 07724, UNITED STATES	
N086034 001 TABLET		RX	APPEF 02-NOV-1987 5MG
WATSON LABORATORIES INC		465 INDUSTRIAL WAY WEST, EATONTOWN, NJ, 07724, UNITED STATES	
ISOSORBIDE DINITRATE		RX	APPEF 29-OCT-1987 10MG
ISOSORBIDE DINITRATE	SUBLINGUAL	311 BONNIE CIR, BOX 1900, CORONA, CA, 928801900, UNITED STATES	
N086054 001 TABLET		RX	APPEF 06-JAN-1988 5MG
WEST WARD PHARMACEUTICAL CORP		465 INDUSTRIAL WAY WEST, EATONTOWN, NJ, 07724, UNITED STATES	
ISOSORBIDE DINITRATE		RX	APPEF 29-OCT-1987 2.5MG
ISOSORBIDE DINITRATE	SUBLINGUAL	465 INDUSTRIAL WAY WEST, EATONTOWN, NJ, 07724, UNITED STATES	
N086055 001 TABLET		RX	APPEF 02-NOV-1987 5MG
WEST WARD PHARMACEUTICAL CORP		465 INDUSTRIAL WAY WEST, EATONTOWN, NJ, 07724, UNITED STATES	
ISOSORBIDE DINITRATE		RX	APPEF 29-OCT-1987 10MG
ISOSORBIDE DINITRATE	ORAL	465 INDUSTRIAL WAY WEST, EATONTOWN, NJ, 07724, UNITED STATES	
N086066 001 TABLET		RX	APPEF 29-OCT-1987 10MG
WEST WARD PHARMACEUTICAL CORP		465 INDUSTRIAL WAY WEST, EATONTOWN, NJ, 07724, UNITED STATES	
ISOSORBIDE DINITRATE		RX	APPEF 29-OCT-1987 10MG
ISOSORBIDE DINITRATE	ORAL	465 INDUSTRIAL WAY WEST, EATONTOWN, NJ, 07724, UNITED STATES	
N086067 001 TABLET		RX	APPEF 29-OCT-1987 10MG

WEST WARD PHARMACEUTICAL CORP ISOSORBIDE DINITRATE	465 INDUSTRIAL WAY WEST, EATONTOWN, NJ, 07724, UNITED STATES
N086166 002 TABLET	APPEF 29-OCT-1987
MUTUAL PHARMACEUTICAL CO INC	SMG
ISOSORBIDE DINITRATE	1100 ORTHODOX ST, PHILADELPHIA, PA, 19124, UNITED STATES
ISOSORBIDE DINITRATE	APPEF 19-SEP-1986 DISCN 12-SEP-1996
ISOSORBIDE DINITRATE	SMG
N086167 001 TABLET	1100 ORTHODOX ST, PHILADELPHIA, PA, 19124, UNITED STATES
MUTUAL PHARMACEUTICAL CO INC	APPEF 19-SEP-1986 DISCN 12-SEP-1996
ISOSORBIDE DINITRATE	20MG
ISOSORBIDE DINITRATE	1100 ORTHODOX ST, PHILADELPHIA, PA, 19124, UNITED STATES
ISOSORBIDE DINITRATE	APPEF 18-SEP-1986 DISCN 12-SEP-1996
ISOSORBIDE DINITRATE	SMG
N086169 001 TABLET	1100 ORTHODOX ST, PHILADELPHIA, PA, 19124, UNITED STATES
MUTUAL PHARMACEUTICAL CO INC	APPEF 19-SEP-1986 DISCN 12-SEP-1996
ISOSORBIDE DINITRATE	10MG
ISOSORBIDE DINITRATE	2555 WEST MIDWAY BLVD, BROOMFIELD, CO, 800380446, UNITED STATES
ISOSORBIDE DINITRATE	APPEF 07-JAN-1988
ISOSORBIDE DINITRATE	SMG
N086222 001 TABLET	2555 WEST MIDWAY BLVD, BROOMFIELD, CO, 800380446, UNITED STATES
SANDOZ INC	APPEF 19-FEB-1988
ISOSORBIDE DINITRATE	SMG
ISOSORBIDE DINITRATE	2555 WEST MIDWAY BLVD, BROOMFIELD, CO, 800380446, UNITED STATES
ISOSORBIDE DINITRATE	APPEF 07-JAN-1988
ISOSORBIDE DINITRATE	10MG
N086223 001 TABLET	2555 WEST MIDWAY BLVD, BROOMFIELD, CO, 800380446, UNITED STATES
SANDOZ INC	APPEF 19-FEB-1988
ISOSORBIDE DINITRATE	SMG
ISOSORBIDE DINITRATE	2555 WEST MIDWAY BLVD, BROOMFIELD, CO, 800380446, UNITED STATES
ISOSORBIDE DINITRATE	APPEF 19-FEB-1988
ISOSORBIDE DINITRATE	2.5MG
N086225 001 TABLET	1800 CONCORD PIKE, WILMINGTON, DE, 19850, UNITED STATES
SANDOZ INC	APPEF 21-AUG-1990
ISOSORBIDE DINITRATE	20MG
ISOSORBIDE DINITRATE	WDLAG 17-SEP-2003
N086405 002 TABLET	1 RAM RIDGE RD, SPRING VALLEY, NY, 10977, UNITED STATES
ASTRAZENECA PHARMACEUTICALS LP	APPEF 12-MAR-1987
SORBITRATE	SMG
ISOSORBIDE DINITRATE	1 RAM RIDGE RD, SPRING VALLEY, NY, 10977, UNITED STATES
ISOSORBIDE DINITRATE	APPEF 12-MAR-1987
ISOSORBIDE DINITRATE	10MG
N086923 001 TABLET	1 RAM RIDGE RD, SPRING VALLEY, NY, 10977, UNITED STATES
PAR PHARMACEUTICAL INC	APPEF 12-MAR-1987
ISOSORBIDE DINITRATE	10MG
ISOSORBIDE DINITRATE	1 RAM RIDGE RD, SPRING VALLEY, NY, 10977, UNITED STATES
ISOSORBIDE DINITRATE	APPEF 12-MAR-1987
ISOSORBIDE DINITRATE	10MG
N086925 001 TABLET	1 RAM RIDGE RD, SPRING VALLEY, NY, 10977, UNITED STATES
PAR PHARMACEUTICAL INC	APPEF 12-MAR-1987
ISOSORBIDE DINITRATE	10MG
ISOSORBIDE DINITRATE	1 RAM RIDGE RD, SPRING VALLEY, NY, 10977, UNITED STATES
ISOSORBIDE DINITRATE	APPEF 12-MAR-1987
ISOSORBIDE DINITRATE	10MG
N087537 001 TABLET	1 RAM RIDGE RD, SPRING VALLEY, NY, 10977, UNITED STATES
PAR PHARMACEUTICAL INC	APPEF 12-MAR-1987
ISOSORBIDE DINITRATE	10MG

ISOSORBIDE DINITRATE	RX	APPEF 02-OCT-1987	
ISOSORBIDE DINITRATE		20MG	
N087545 001 TABLET			
MUTUAL PHARMACEUTICAL CO INC			1100 ORTHODOX ST, PHILADELPHIA, PA, 19124, UNITED STATES
ISOSORBIDE DINITRATE	RX		
ISOSORBIDE DINITRATE			
ISOSORBIDE DINITRATE			
N087564 001 TABLET			
MUTUAL PHARMACEUTICAL CO INC			1100 ORTHODOX ST, PHILADELPHIA, PA, 19124, UNITED STATES
ISOSORBIDE DINITRATE	RX		
ISOSORBIDE DINITRATE			
ISOSORBIDE DINITRATE			
N087946 001 TABLET			
PAR PHARMACEUTICAL INC			1 RAM RIDGE RD, SPRING VALLEY, NY, 10977, UNITED STATES
ISOSORBIDE DINITRATE	RX		
ISOSORBIDE DINITRATE			
ISOSORBIDE DINITRATE			
N088088 001 TABLET			
WEST WARD PHARMACEUTICAL CORP			465 INDUSTRIAL WAY WEST, EATONTOWN, NJ, 07724, UNITED STATES
ISOSORBIDE DINITRATE	RX		
ISOSORBIDE DINITRATE			
ISOSORBIDE DINITRATE			
N088124 001 TABLET			
ASTRAZENECA PHARMACEUTICALS LP			1800 CONCORD PIKE, WILMINGTON, DE, 19850, UNITED STATES
SORBITRATE	RX		
ISOSORBIDE DINITRATE			
ISOSORBIDE DINITRATE			
N088125 001 TABLET			
ASTRAZENECA PHARMACEUTICALS LP			1800 CONCORD PIKE, WILMINGTON, DE, 19850, UNITED STATES
SORBITRATE	RX		
ISOSORBIDE DINITRATE			
ISOSORBIDE DINITRATE			
N089190 001 TABLET			
SUPERPHARM CORP			155 OVAL DR, CENTRAL ISLIP, NY, 11722, UNITED STATES
ISOSORBIDE DINITRATE	RX		
ISOSORBIDE DINITRATE			
ISOSORBIDE DINITRATE			
N089191 001 TABLET			
SUPERPHARM CORP			155 OVAL DR, CENTRAL ISLIP, NY, 11722, UNITED STATES
ISOSORBIDE DINITRATE	RX		
ISOSORBIDE DINITRATE			
ISOSORBIDE DINITRATE			
N089192 001 TABLET			
SUPERPHARM CORP			155 OVAL DR, CENTRAL ISLIP, NY, 11722, UNITED STATES
ISOSORBIDE DINITRATE	RX		
ISOSORBIDE DINITRATE			
ISOSORBIDE DINITRATE			
N089367 001 TABLET			
SANDOZ INC			2555 WEST MIDWAY BLVD, BROOMFIELD, CO, 800380446, UNITED STATES
ISOSORBIDE DINITRATE	RX		
ISOSORBIDE DINITRATE			
ISOSORBIDE DINITRATE			

D

[54] METHOD OF REDUCING MORTALITY ASSOCIATED WITH CONGESTIVE HEART FAILURE USING HYDRALAZINE AND ISOSORBIDE DINITRATE

[76] Inventor: Jay N. Cohn, 4848 Russel Av. S., Minneapolis, Minn. 55410

[21] Appl. No.: 41,210

[22] Filed: Apr. 22, 1987

[51] Int. Cl. A61K 31/34; A61K 31/50

[52] U.S. Cl. 514/248; 514/470

[58] Field of Search 514/248, 470

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Primary Examiner—Allen J. Robinson

Attorney, Agent, or Firm—Merchant, Gould, Smith,

Edell, Welter & Schmidt

[57] ABSTRACT

A method of reducing mortality associated with chronic congestive heart failure in a patient with impaired cardiac function and concomitant reduced exercise tolerance, comprising the oral administration to said patient in need of the same of a combination of (a) between about 75 and about 300 milligrams of hydralazine, per day and (b) between about 40 and about 160 milligrams of isosorbide dinitrate, per day.

2 Claims, No Drawings

**METHOD OF REDUCING MORTALITY
ASSOCIATED WITH CONGESTIVE HEART
FAILURE USING HYDRALAZINE AND
ISOSORBIDE DINITRATE**

BACKGROUND OF THE INVENTION

The work which resulted in the present invention was supported by the Cooperative Studies Programs of the Medical Research Services, Veterans Administration Central Office, Washington, D.C.

The present invention relates to a method of reducing the incidence of mortality associated with chronic congestive heart failure in patients, by administering to such patients an effective amount of a combination of hydralazine, or a pharmaceutically acceptable salt thereof, and isosorbide dinitrate.

Hydralazine, or 1-hydrazinophthalazine, and the pharmaceutically acceptable acid addition salts thereof is disclosed in U.S. Pat. No. 2,484,029 which issued Oct. 11, 1949. Hydralazine, in the form of its hydrochloride salt, is a widely used arteriolar dilator drug indicated for use in the treatment of essential hypertension. Although hydralazine hydrochloride has been found to exert a sustained hemodynamic effect in patients with chronic congestive heart failure, studies have not confirmed that this drug can increase exercise tolerance or relieve symptoms when given alone, as see Chatterjee et al., *Ann. Intern. Med.*, Vol. 92, pp. 600-604 (1980) and Franciosa et al., *Am. Heart J.*, Vol. 104, pp. 587-594 (1982).

Isosorbide dinitrate, or 1,4:3,6-dianhydrosorbitol 2,5-dinitrate, is a widely used peripheral dilator, producing a vasodilatory effect on both peripheral arteries and veins with predominant effects on the latter. Isosorbide dinitrate is indicated for the treatment and prevention of angina pectoris and may be symptomatically effective in improving the exercise capacity of patients suffering from chronic congestive heart failure, as see C. V. Leier et al., *Circulation*, Vol. 67, pp. 817-822 (1983).

The rationale for vasodilator therapy for heart failure is evidence that vasoconstriction in the systemic arterial and venous beds raises impedance to left ventricular ejection and shifts blood centrally from the venous capacitance vessels. The results of these circulatory effects is increased preload and afterload that adversely affect left ventricular performance and contribute to low cardiac output and venous congestion that characterize heart failure.

The combined use of hydralazine hydrochloride and isosorbide dinitrate has been suggested in the vasodilator therapy of patients with chronic heart failure and for the purpose of eliciting a favorable symptomatic hemodynamic effect on left ventricular performance, as see B. Massie et al., *Am. J. Cardiol.*, Vol. 40, pp. 794-801 (1977) and G. L. Pierpont et al., *Chest*, Vol. 73, pp. 8-13 (1978).

Prazosin hydrochloride, an alpha-adrenoceptor antagonist indicated for the treatment of hypertension, has likewise been suggested in the vasodilator therapy of patients with chronic heart failure and for the purpose of eliciting a favorable symptomatic hemodynamic effect on left ventricular performance, as see N. A. Awan et al., *Am. J. Med.*, Vol. 71, pp. 153-160 (1981) and W. S. Colucci et al., *Am. J. Cardiol.*, Vol. 45, pp. 337-344 (1980).

However, in neither the studies conducted with prazosin hydrochloride, nor the studies conducted with a combination of hydralazine hydrochloride and isosorbide dinitrate, has any influence on mortality been established.

It has now been surprisingly and unexpectedly discovered that while no statistically significant reduction in mortality could be established using prazosin hydrochloride in vasodilator therapy in chronic congestive heart failure, a combination of hydralazine hydrochloride and isosorbide nitrate has been formed to substantially and significantly reduce the incidence of mortality in such patients.

It is therefor an object of the present invention to provide a method of reducing the incidence of mortality associated with chronic congestive heart failure in patients by orally administering a combination of hydralazine, or a pharmaceutically acceptable salt thereof, and isosorbide dinitrate to such patients in need of the same.

It is a further object of the present invention to provide compositions containing hydralazine or a pharmaceutically acceptable salt thereof, and isosorbide dinitrate for use in such method.

These and other objects of the present invention are apparent from the following detailed disclosures.

**DETAILED DESCRIPTION OF THE
INVENTION**

One embodiment of the present invention relates to a method of reducing mortality associated with chronic congestive heart failure in a patient with impaired cardiac function and concomitant reduced exercise tolerance, comprising the oral administration to said patient in need of the same of a combination of (a) between about 75 and about 300 milligrams of hydralazine or a pharmaceutically acceptable acid addition salt thereof, per day, and (b) between about 40 and about 160 milligrams of isosorbide dinitrate, per day.

By impaired cardiac function in such patient is meant a patient exhibiting abnormal cardiac dilatation, as evidenced, for example, either by a cardiothoracic ratio greater than about 0.55 on a chest X-ray film or by a left ventricular internal diameter diastole greater than about 2.7 centimeter per square meter on echocardiography, or a patient exhibiting left ventricular functional impairment, as evidenced, for example, by a radionuclide ejection fraction less than about 45 percent.

Reduced exercise tolerance in such patient can be assessed by methods known in the art. For example, a convenient assessment can be made by a progressive maximal bicycle-ergometer exercise test taken while expired air is collected continuously to monitor oxygen consumption, with a peak of generally less than about 25 ml per kilogram of patient body weight per minute. Reduced exercise tolerance is measured by patient breathlessness and fatigue.

In a preferred embodiment of the present invention, the patient with chronic congestive heart failure is additionally treated with digitalis, such as digoxin, preferably orally, to achieve a steady state blood serum concentration of the same of at least about 0.7 nanograms per ml, preferably between about 0.7 and about 2.0 nanograms per ml.

Also, in preferred embodiment of the present invention, the patient with chronic congestive heart failure is additionally placed on a regimen of conventional diuretic therapy to manage edema. Depending upon the diuretic employed, potassium chloride may be administered to the patient in order to optimize the fluid balance while avoiding hypokalemic alkalosis. Preferably,

the diuretic therapy is achieved by oral administration of the diuretic, and potassium chloride as needed. Suitable conventional diuretics include, for example, thiazides such as chlorothiazide (about 500 to about 2000 mg orally per day), hydrochlorothiazide (about 50 to about 200 mg orally per day), ethacrynic acid (about 50 to about 400 mg orally per day), furosemide (about 40 to about 200 mg, 1, 2 or 3 times per day), spironolactone (about 25 to about 50 mg orally twice to four times per day), or triamterene (about 50 to about 100 mg orally one to four times per day), or conventional combinations thereof. Where potassium therapy is indicated to prevent hypokalemia, the daily ingestion of foods with high potassium content may be sufficient, such as bananas or orange juice, but potassium chloride in liquid or solid form, e.g. between about 20 to 40 milliequivalents potassium chloride two to four times per day, may be necessary.

The hydralazine may be generally administered in the form of its pharmaceutically acceptable acid addition salt, preferably the hydrochloride salt thereof.

The two ingredients, the hydralazine, or pharmaceutically acceptable salt thereof, and the isosorbide dinitrate, may be orally administered together in the form of a combined unit dose form, or separately, as individual dose forms.

The per diem regimen of the hydralazine and isosorbide dinitrate, for oral administration, is conveniently met, for example, by administering the hydralazine in a unit dose form of a 37.5 milligram capsule orally twice daily up to two such capsules four times daily, and by administering the isosorbide dinitrate as a 20 milligram tablet unit dose form, and orally administering between one-half of such tablet four times a day to two tablets four times a day.

Preferably, therapy is begun by administering 37.5 mg hydralazine, e.g. in the form of its hydrochloride, four times per day and 20 mg isosorbide dinitrate four times per day. In the absence of side effects, the dosage can be increased to 75 mg hydralazine hydrochloride and 40 mg isosorbide dinitrate, each given four times per day. If drug related side effects occur, the dosage is reduced to 10 mg of isosorbide dinitrate administered four times daily, and 37.5 mg hydralazine administered twice daily. Where dose reduction occurs, an attempt may be made at a later date to reinstate a higher dose regimen.

The combination regimen as described above is intended over a long period. Using this regimen a surprising statistically significant reduction in mortality associated with chronic congestive heart failure in such patients can be achieved during the course of administration.

In order to achieve the objective of the invention, the patient suffering from congestive heart failure should advantageously be placed on the combination therapy for a period preferably in excess of six months, more preferably in excess of one year and most preferably in excess of two years.

The following Example is for illustrative purposes only and is not intended to limit the metes and bounds of the present invention.

EXAMPLE

A total of 642 male patients between the ages of 18 and 75, with chronic congestive heart failure, having impaired cardiac function and reduced exercise tolerance and undergoing conventional treatment with di-

goxin (>0.7 ng per milliliter) and diuretics to optimize fluid balance were entered into a double-blind trial of three groups, one group (183 patients) to receive additional treatment with prazosin, one group (186 patients) to receive a combination of hydralazine hydrochloride and isosorbide dinitrate, and one group (273 patients) to receive placebo. The groups continued their regimen of optimal dose of digoxin and diuretic therapy throughout the study. The placebo group also received placebo tablets and placebo capsules taken four times daily. The prazosin group took prazosin hydrochloride capsules, 2.5 mg, and placebo tablets four times daily. The remaining group was given 37.5 mg of hydralazine hydrochloride capsules and 20 mg of isosorbide dinitrate in matching tablets to be taken four times daily. In all groups, therapy began with one capsule and one tablet four times daily. In the absence of side effects, this dose was increased two weeks later to two capsules and two tablets four times daily. If side effects thought to be drug related occurred, the dose was reduced to half a tablet four times daily or to one capsule twice daily. If the dose were reduced, an attempt was made in each case to reinstate the full dose at a later date. Of the 642 patients in the study, 284 (44.2 percent) had coronary disease and 358 (53.8 percent) had heart failure unrelated to coronary disease. The distribution of base-line variables in the three treatment groups was remarkably similar. In the study, follow-up averaged 2.3 years, with a range of 6 months to 5.7 years. During the follow-up period, there were 120 deaths in the placebo group (44.0 percent), 91 deaths in the prazosin group (49.7 percent) and 72 deaths in the hydralazine group (38.7 percent). Among the patients with chronic heart failure who died, it was difficult to exclude the heart condition as a contributing factor to death—even when other serious diseases were present. Therefore, the analysis was confined to mortality from all causes. Of the deaths, 45 percent were classified as "sudden". At one year, the cumulative mortality rate in the group treated with the hydralazine-nitrate combination (12.1 percent) was 38 percent lower than in the placebo group (19.5 percent). For mortality by two years, the risk reduction among patients treated with the hydralazine-nitrate combination was 34 percent ($P < 0.028$). The cumulative mortality rates at two years were 25.6 percent in the hydralazine-isosorbide dinitrate group and 34.3 percent in the placebo group. At three years, the mortality rate was 36.2 percent in the hydralazine-isosorbide dinitrate group and 46.9 percent in the placebo group. The mortality-risk reduction in the hydralazine-isosorbide dinitrate group was 36 percent vis-a-vis the placebo group after three years. In contrast, over the three year period, the mortality rate in the prazosin group was essentially the same as in the placebo group. Other specifics of this study, including comparative base line data, drop-out analyses, cumulative mortality specifics, and hemodynamic variables in the treatment groups are set forth in Cohn et al., *N. Engl. J. Med.*, Vol. 314, pages 1547-62 (June 1986), the disclosure of which is incorporated herein by reference.

What is claimed is:

1. A method of reducing the incidence of mortality associated with chronic congestive heart failure in a patient with impaired cardiac function and concomitant reduced exercise tolerance, comprising the oral administration to said patient in need of the same of a combination of

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- (a) between about 75 and about 300 milligrams of hydralazine, or a pharmaceutically acceptable acid addition salt thereof, per day, and
 - (b) between about 40 and about 160 milligrams of isosorbide dinitrate, per day.
2. A method according to claim 1, wherein said patient is further treated orally with digoxin in an amount

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sufficient to achieve in said patient a blood serum concentration of digoxin of at least about 0.7 nanograms per milliliter and an effective edema managing amount of a pharmaceutically acceptable diuretic selected from the group consisting of thiazides, ethacrynic acid, furosemide, spironalactone and triamterene.

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PATENT NUMBER	FEE AMT	SUR CHARGE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	STAT	ATTY DKT NUMBER
4,868,179	\$465.00	\$0.00	07/041,210	09/19/89	04/22/87	04	YES	PAID	7640.1-US-01

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4,868,179	\$1,025.00	\$0.00	07/041,210	09/19/89	04/22/87	08	YES	PAID	7640.1-US-01

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4,868,179	\$1,495.00	\$0.00	07/041,210	09/19/89	04/22/87	12	YES	PAID	7640.1-US-01

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3/1/93 Submission of original IND for BiDil
 3/2/93 FDA receipt of IND
 3/5/93 Receipt of letter from FDA acknowledging receipt of IND and assigning
 IND number 41,186
 3/15/93 Phone conversation with D. Roeder of FDA re manufacturing of BiDil
 3/16/93 Phone conversation with G. Buehler of FDA re IND review status
 3/19/93 Letter from Medco and telephone conversation re manufacturing of BiDil
 3/29/93 Phone conversation with G. Buehler of FDA re IND review status
 4/1/93 Effective date of IND
 4/6/93 Receipt of fax from G. Buehler of FDA re biopharm comments from IND
 review
 6/4/93 Receipt of FDA letter summarizing pre-IND meeting held on 11/5/92
 7/15/93 Receipt of FDA letter re comments on CMC section of IND
 3/13/94 Phone call from G. Buehler of FDA re waiver of CRF requirements for V-
 HeFT II study
 6/6/94 Submission of 1993 annual report and protocol amendment
 8/8/94 Letter to FDA re referencing Apresoline NDA
 10/25/94 Phone call to T. Ludden of FDA re assay for biopharm studies of
 hydralazine
 10/28/94 Phone call from Dr. Marroum of FDA re assay for CB-01 study
 10/31/94 Teleconference with FDA re pilot BE study and CB-02 study
 10/31/94 Submission of protocol amendment providing for analysis of both free and
 apparent hydralazine and CMC amendment
 11/1/94 Twelve normal subjects enrolled for bioequivalency study
 11/30/94 Submission of pilot study results and preliminary safety data
 12/7/94 Teleconference with FDA re trial design for BE study
 2/9/95 Phone call from G. Buehler re requirements for environmental assessment
 report
 4/17/95 Letter to FDA re proposal for data to be generated for environmental
 assessment
 5/9/95 Phone call to G. Buehler of FDA re V-HeFT II patient summaries
 5/15/95 Teleconference re environmental assessment requirements for BiDil
 5/31/95 Submission of 1994 annual report
 7/27/95 Submission of proposal for stability data to be included in NDA
 8/2/95 Submission of CB-02 protocol and amendment for change in
 manufacturing site
 8/9/95 Phone call to FDA re weight variation criteria for CB-02 study
 8/15/95 Phone call from G. Buehler of FDA re CB-02 and NDA requirements
 8/17/95 Submission of amendment to protocol CB-02 providing for change in
 body weight requirements
 8/23/95 Phone call from G. Buehler re V-HeFT II case report form requirements
 9/1/95 Submission of protocol amendment providing for a change in the oral
 clearance levels of hydralazine
 9/26/95 Receipt of FDA fax re biopharm requirements
 9/29/95 Submission of pre-NDA submission package

9/29/95 Submission of protocol amendment re earlier hydralazine serum sampling; teleconference with FDA re CB-02 amendment re weight requirement

10/5/95 Teleconference with FDA re discussion of bioavailability trial

11/2/95 Phone call from Dr. Burnett of FDA re CB-02 amendment 4

11/3/95 Letter from FDA re confirming acceptance of weight variation in CB-02

11/10/95 Submission of response to FDA fax of 9/26/95 re biopharm data

11/30/95 Teleconference with FDA re multi dose kinetic study for higher doses

12/15/95 Letter from N. Morgenstern of FDA summarizing biopharmaceutics review of CB-02

1/19/96 Phone call to G. Buehler of FDA re manufacturing review prior to NDA submission

6/25/96 Payment of user fee for NDA

7/1/96 Letter from FDA re receipt of user fee

7/3/96 Filing of New Drug Application and methods validation

7/10/96 Letter from FDA re receipt of methods validation

7/12/96 Phone call from Gary Buehler of FDA re NDA filing

7/15/96 Letter from FDA re receipt of NDA submission

7/29/96 Phone call from Gary Buehler of FDA requesting protocol for multi dose kinetic study and electronic version of NDA

8/9/96 Submission of draft protocol for multi dose pharmacokinetic study

8/12/96 Submission of additional datasets for clinical studies in NDA

8/13/96 Submission of environmental assessment certification for BiDil; Phone call from FDA re environmental assessment for BiDil; Phone call to FDA re review team and review classification

8/21/96 Fax from G. Buehler of FDA re FDA comments on multi dose study

9/3/96 Phone conversation with Dr. Marroum of FDA re multi dose study design

9/10/96 Letter from FDA re manufacturing and controls deficiencies

9/12/96 Submission of patent information

9/13/96 Phone call from G. Buehler of FDA re FDA preference for multi dose study design

9/20/96 Fax from FDA re method validation for BiDil; Medco response re method validation samples

9/26/96 Letter to FDA re update of method validation studies

9/26/96 Response to FDA manufacturing and controls deficiency letter

9/30/96 Phone call from N. Falcone of FDA re receipt of method validation samples

10/11/96 Phone call from G. Buehler of FDA re rescheduling meeting re multi dose study design

10/15/96 Phone conversation with G. Buehler re meeting re multi dose study design

10/24/96 Submission of NDA Safety Update Report

10/28/96 Phone call from C. Ganley at FDA re statistical treatment of patients discontinued from study early

10/30/96 Phone call to G. Buehler of FDA re multi dose protocol and BiDil trade name

11/4/96 Fax to FDA re multi dose protocol meeting

11/18/96 Phone call to G. Buehler of FDA re meeting with FDA re advisory committee

11/20/96 Letter to FDA re follow-up with patients who discontinued study early

11/21/96 Submission of published mechanistic data to FDA

11/21/96 Letter from FDA re manufacturing and controls deficiencies

11/21/96 Meeting with review division, Medco presented with FDA questions

11/25/96 Telephone conversation with Dr. Marroum of FDA re dissolution testing

11/26/96 Letter to FDA re summary of issues needed to be addressed prior to advisory committee meeting

11/27/96 Fax to FDA re composition and specification of BiDil tablets; Phone call from Dr. Marroum of FDA re multi dose study protocol

12/4/96 Phone call to G. Buehler re CMC deficiency letter

12/11/96 Submission re response to medical/statistical reviewers questions posed at meeting on 11/21/96

12/12/96 Letter to FDA re response to CMC deficiency letter; call from G. Buehler of FDA re supplemental analyses

12/13/96 Submission to FDA re response to medical/statistical reviewers

12/18/96 Letter to FDA re response to reviewers concern over trade name

12/26/96 Fax to FDA re November 25, 1985 IND amendment

1/2/97 Submission re response to questions posed by medical/statistical reviewers by fax on 12/23/96

1/2/97 Submission re minutes prepared for V-HeFT I trial data presentations

1/9/97 Memo to G. Buehler of FDA re published animal studies on nitrate tolerance mechanism

1/9/97 Fax from FDA re Dr. Ganley's draft medical/statistical review

1/13/97 Submission to FDA re additional statistical analyses requested by FDA

1/16/97 Phone conversation with G. Buehler of FDA re advisory committee packages

1/17/97 Teleconference with FDA re clinical study report, nitrate tolerance, subgroup analysis, PK data, and dissolution data

1/21/97 Phone call to G. Buehler of FDA re dissolution data requested by FDA

1/23/97 Submission responding to FDA's request for raw pharmacokinetic data and statistical analysis output from multi dose study; submission of subset analysis information and method of imputing missing data for ejection fraction

1/27/97 Submission of Advisory Committee briefing document

1/27/97 Submission of statistical output data for study CB-02

1/28/97 Conference call with FDA re advisory committee briefing document contents

1/31/97 Submission of revised advisory committee briefing document

2/3/97 Submission re requested additional dissolution testing

2/6/97 Submission of additional advisory committee materials to advisory committee

2/7/97 Fax to FDA re statistical addendum to advisory committee materials

2/12/97 Submission to FDA re addendum to the 2/3/97 dissolution submission

2/14/97 Fax from FDA re draft questions for advisory committee

2/19/97 Receipt of FDA addendum to FDA review for advisory committee
 2/24/97 Submission to FDA re corrected electronic output for study CB-02; addendum to advisory committee briefing document
 2/24/97 Receipt of FDA overview of animal studies examining nitrate tolerance
 2/25/97 Submission of presentation outline for advisory committee
 2/27/97 Cardiovascular and Renal Drugs Advisory Committee meeting
 3/10/97 Phone conversation with G. Buehler of FDA re FDA review activities
 3/18/97 Phone conversation with G. Buehler of FDA re approvability of BiDil
 3/25/97 Phone conversation with G. Buehler of FDA re chemistry deficiencies
 4/14/97 Letter to FDA re agenda for meeting 4/22/97
 4/22/97 Meeting with FDA re outcome of advisory committee meeting
 7/2/97 Receipt of not approvable letter from FDA
 7/16/97 Letter to FDA re intent to file an amendment in response to not approvable letter
 8/15/97 FDA letter to Medco re user fee payment due
 9/8/97 Payment of user fee balance
 7/21/99 Meeting with FDA re not approvable letter
 8/13/99 Meeting between Dr. Jay Cohn and FDA re status of NDA and subset analyses
 9/8/99 Transfer of ownership of NDA to NitroMed, Inc.
 9/24/99 FDA letter to NitroMed confirming transfer of ownership of NDA
 3/13/00 Submission to FDA re pre-meeting materials for meeting to discuss not approvable letter
 4/5/00 Meeting with FDA re data needed to support an indication for the treatment of heart failure in black patients
 7/25/00 Letter to FDA responding to questions from 4/5/00 meeting
 7/28/00 Amendment to NDA responding to not approvable letter
 10/10/00 Letter to FDA re meeting request to discuss 7/28/00 amendment
 12/12/00 Meeting with FDA re discussion of new protocol for study in black patients with heart failure
 12/20/00 Letter to FDA from Dr. Jay Cohn re protocol for phase III study
 1/5/01 Submission of revised outline of proposed study in black patients with heart failure
 1/8/01 Letter to FDA re USP specification changes
 1/11/01 Receipt of FDA minutes of 12/12/00 meeting
 1/19/01 Submission of protocol modifications in response to investigator meeting
 1/23/01 Teleconference with FDA re CMC deficiencies in not approvable letter
 1/24/01 Teleconference with FDA re FDA feedback on draft protocol outline
 1/29/01 Submission of revised statistical protocol
 3/1/01 Letter from FDA stating a single positive study would be a basis of approval of BiDil for heart failure in blacks
 4/6/01 Teleconference with FDA re discussion of clinical protocol for treatment of blacks with heart failure
 4/16/01 Fax from FDA re biopharm comments in response to 1/8/01 submission
 5/3/01 Submission of protocol amendment
 6/15/01 Submission of second protocol amendment and investigator information

8/1/01 Submission of third protocol amendment and additional investigator information

8/28/01 Submission of additional investigator information

9/26/01 Submission of additional investigator information

10/18/01 Submission of additional investigator information

12/06/01 Phone call to E. Fromm of FDA re IND

12/12/01 A-HeFT protocol amendment to clarify the inclusion criteria

1/9/02 Phone conversation with E. Fromm re transfer of IND

1/15/02 Amendment to NDA re transfer of IND

2/1/02 Receipt of FDA confirmation of IND transfer

2/1/02 Letter from FDA waiving 30 day waiting period for reactivated IND

5/9/02 Phone call to E. Fromm of FDA re A-HeFT statistical plan

5/28/02 Teleconference with FDA re addition of a second interim analysis to the statistical plan

5/29/02 Amendment to IND re statistical plan

6/3/02 Amendment to IND re CMC update

6/4/02 Amendment to IND re annual report

6/12/02 Amendment to IND re new investigators

6/25/02 Teleconference with FDA re CMC deficiencies in not approvable letter

8/16/02 Amendment to IND re statistical plan

10/23/02 Amendment to IND re limiting on-study duration in A-HeFT to 18 months

11/6/02 Phone call from E. Fromm of FDA re acceptability of 18 month protocol amendment

11/8/02 Teleconference with FDA re statistical analysis and recruitment

2/3/03 Response to FDA CMC question regarding degradants

3/25/03 Amendment to IND re interim analysis and sample size adjustment

5/20/03 Amendment to IND re annual report

6/13/03 Request for biowaiver for second strength of tablets

7/25/03 Phone call from FDA re request for additional information re request for biowaiver

7/30/03 Submission re additional information requested for biowaiver

8/5/03 Fax from FDA re biopharm reviewer's comments for biowaiver request

8/19/03 Response to FDA's 8/5/03 comments re biowaiver

8/26/03 Amendment to IND re protocol exclusion of patients taking erectile dysfunction medications

6/9/04 Amendment to IND re steering committee membership

7/21/04 IND amendment re extension of A-HeFT trial

8/3/04 Meeting with FDA re DSMB recommendation to stop A-HeFT trial early due to statistically significant benefit over placebo

9/28/04 Letter to FDA re review of proposed trade name

10/5/04 Amendment to IND re CMC pre-NDA meeting

10/6/04 Resubmission of V-HeFT I and II analyses in blacks

11/3/04 Letter to FDA re comments on A-HeFT statistical analysis plan

12/10/04 Submission of patent information

12/21/04 Submission of proposed package insert

12/23/04 Payment of user fee

1/4/05 Submission of revised package insert
1/7/05 Submission of labeling amendment
2/1/05 Amendment to IND re initial safety report
2/3/05 Letter from FDA acknowledging resubmission of NDA and waiver and deferral of pediatric information

3/11/05 Amendment to IND re initial safety report
3/18/05 Amendment to IND re new investigators in A-HeFT extension trial
3/22/05 Submission re responses to FDA biostatistician questions
3/28/05 Amendment to IND re initial safety report; follow-up safety report
4/4/05 Fax from FDA re advisory committee meeting for BiDil
4/7/05 Submission of proposed package labeling for BiDil
4/11/05 Response to FDA medical reviewer questions
4/15/05 Response to FDA biostatistics questions
4/22/05 Response to FDA medical reviewer questions
4/25/05 Response to FDA biostatistics questions
4/26/05 Submission of NDA four-month safety update report
4/27/05 Response to FDA chemistry questions
4/29/05 Response to FDA clinical questions
5/6/05 Submission of pediatric drug development plan and request for pediatric waiver

5/9/05 Response to FDA biostatistics comments
5/11/05 Receipt of CMC discipline review letter
5/13/05 Receipt of draft advisory committee questions
5/19/05 Submission of sponsor advisory committee briefing document
5/20/05 Submission of reference publications for advisory committee briefing document

5/25/05 Receipt of pediatric waiver for entire pediatric population
6/3/05 Amendment to IND re annual report
6/9/05 Response to FDA CMC deficiencies received in 5/11/05 discipline review letter

6/10/05 Submission re claimed exclusivity for BiDil
6/21/05 Submission re assessment of quality of life
6/23/05 FDA approval of BiDil