

CLINICAL REVIEW

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Reviewer Name	Salma Lemtouni
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Established Name	Hydralazine HCl and Isosorbide dinitrate
(Proposed) Trade Name	BiDil
Applicant	NitroMed, Inc.
Priority Designation	P
Formulation	Hydralazine 75 mg/Isosorbide dinitrate 40 mg
Dosing Regimen	t.i.d.
Indication	Heart Failure
Intended Population	African American

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Abbreviations

MLWHF:	Minnesota Living with Heart Failure Questionnaire
QOL:	quality of life
HYD:	hydralazine
ISDN:	isosorbide dinitrate
CHF:	congestive heart failure
COPD:	chronic obstructive pulmonary disease
DVT:	deep venous thrombosis
TIA:	transient ischemic attack
AE:	adverse event
EF:	ejection fraction

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Addendum to the A-HeFT review

1 CORRECTIONS

Control-treatment-category headings were reversed in the original review (Tables 2 and 3, page 14)

Table 1. V-HeFT I Data Summary Table¹

	Blacks N = 56			Whites N = 141			Racial Interaction p-Value
	BiDil	Placebo	p-Value	BiDil	Placebo	p-Value	
Annual Mortality Rate (%)	9.7	17.3	0.04	16.9	18.8	ns	0.11
Mortality Risk Ratio	0.341	N/A	0.004	0.746	N/A	0.11	0.074
Change in EF at 12 Months vs. Baseline (%)	0.023	0.0136	0.82	0.081	0.012	0.02	0.23
Change in MVO ₂ at 12 M (mL/kg/min)	1.25	-0.394	0.068	0.681	-0.162	0.12	0.69

Table 2. V-HeFT II Data Summary Table

	Blacks N = 215			Whites N = 574			Racial interaction p-value
	BiDil	Enalapril	p-value	BiDil	Enalapril	p-value	
Annual Mortality Rate (%)	12.9	12.8	ns	14.9	11.0	0.02	0.25
Mortality Risk Ratio	0.95	N/A	0.83	1.48	N/A	0.0087	0.10
Change in EF @ 12 M (%)	2.97	1.32	0.34	3.86	2.48	0.12	0.82
Change in MVO ₂ at 12 M (mL/kg/min)	0.79	0.01	0.15	0.24	-0.42	0.058	0.47
Change in QOL at 12 M	-0.67	1.04	0.04	0.24	0.26	0.97	0.09

2 CLARIFICATIONS

The following are missing in the original review

2.1 Blood Pressure Measurement in A-HeFT

Blood pressure was measured at each patient visit; patient study visits were scheduled to occur at times convenient for the patient and clinical site personnel, and did not take into account how recently the patient had taken his/her prior study medication dose.

2.2 Statistical Allocation to the Secondary Endpoints

No statistical weight was allocated to the secondary endpoints.

¹ Analyses completed by the sponsor

2.3 Minnesota Living with Heart Failure Questionnaire

Table 3. The Minnesota Living with Heart Failure (MLWHF) Questionnaire

Did your heart failure prevent you from living as you wanted during the last month by:		No	Very little				Very much
		0	1	2	3	4	5
1	Causing swelling in your ankles, legs etc.?	0	1	2	3	4	5
2P	Making you sit or lie down to rest during the day?	0	1	2	3	4	5
3P	Making your walking about or climbing stairs difficult?	0	1	2	3	4	5
4P	Making your Working Around the house or yard difficult?	0	1	2	3	4	5
5P	Making your going places away from home difficult?	0	1	2	3	4	5
6P	Making your sleeping well at night difficult	0	1	2	3	4	5
7P	Making your sleeping to or doing things with your friend s or family difficult?	0	1	2	3	4	5
8	Making your working to earn a living difficult?	0	1	2	3	4	5
9	Making your recreational pastimes, sports or hobbies difficult	0	1	2	3	4	5
10	Making you sexual activities more difficult?	0	1	2	3	4	5
11	Making you eat less of the foods you like?	0	1	2	3	4	5
12P	Making you short of breath?	0	1	2	3	4	5
13P	Making you tired, fatigued, or low on energy?	0	1	2	3	4	5
14	Making you stay in a hospital?	0	1	2	3	4	5
15	Costing you money for medical care?	0	1	2	3	4	5
16	Giving you side effects from medications?	0	1	2	3	4	5
17E	Making you feel you are a burden to your family or friends?	0	1	2	3	4	5
18E	Making you feel a loss of self-control in your life?	0	1	2	3	4	5
19E	Making you worry?	0	1	2	3	4	5
20E	Making it difficult for you to concentrate or remember things?	0	1	2	3	4	5
21E	Making you feel depressed?	0	1	2	3	4	5
The QOL questionnaire, per publication consists of four dimensions:							
1 global score (all questions);							
2 physical dimension score (questions # 2-7 and 12 and 13);							
3. emotional dimension (Questions 17-21) and							
4. economic dimension;							

Copyright University of Minnesota 1986:

Rector, TS; Kubo, SH and Cohn, JN; " Content, Reliability and Validity of a New Measure, The Minnesota Living with Heart Failure Questionnaire; Heart Failure, 1987; 198-209.

E-Emotional component

P-Physical Dimension

2.4 Other Trials

An Open label, non-controlled extension trial of BiDil (X-A-HeFT) is in progress. All 1050 patients who have participated in A-HeFT were to be offered the option to enroll in X-A-HeFT. The overall objective was to demonstrate continued safety and tolerability, and to assess compliance with treatment for the duration of 12 months. BiDil was to be given to a target dose of 225/120 mg of HYD/ISDN.

3 SAFETY ADDENDUM

3.1 X-A-HeFT Four-Month Safety Update

3.1.1 Background

As of April 8 2005, 187 subjects have continued onto X-A-HeFT and generated the safety data discussed below. The extent of exposure was not provided and only a listing of patients with serious AEs was.

3.1.2 Adverse Events

--two deaths, one cardiac arrest and the other unspecified;

--hospitalization for:

-CHF exacerbation in 2;

-exacerbation of cardiomyopathy in 2;

-pneumonia in 4;

-worsening of COPD in 2;

-other respiratory in 4;

-acute renal failure in 1;

-other: chest pain in 1, TIA in 1, mental in 2, DVT in 1, bone fracture in 1 and acute gastroenteritis in 1;

3.1.3 Comments

This information does not add much to the interpretation of the safety profile of BiDil because there is no comparison group and the population studied is very sick and it is not unlikely to observe the AEs listed above.

3.2 CB-01 and CB-02

Safety summary of these two studies is missing in the original review, and the following summary was taken from Dr. Hinderling's review.

3.2.1 CB-01

A single dose of BiDil given as a fixed combination of 37.5 mg/ 20 mg b.i.d. was compared to the same dose given, in two formulations, as HYD tablet and ISDN tablet , and as HYD capsule and ISDN tablet. Twelve healthy subjects were randomized into the three formulation groups in a three-period crossover design with a 7 day wash out period.

There were two cases of serious postural hypotension, and 9 out of 12 subjects refused to progress to the next treatment period as a result of adverse events. Headache was reported by 10 subjects. The study was terminated early

3.2.2 CB-02

The bioavailability of low and high doses (37.5/10 mg and 75/40 mg tablets) of a fixed combination of HYD and ISDN were compared to HYD 37.5 mg tablet plus ISDN 10 mg tablet and HYD 37.5 mg capsule plus ISDN 10 mg tablet in 149 healthy males and females who have

been initiated on a single dose of HYD HCl 37.5 mg/ISDN 10 mg solution. Of the 88 subjects who were identified as slow acetylators, 75 were randomized to participate in Phase B. In Phase B subjects were randomized into groups A (low fixed dose), B (tablet/tablet formulation), C (capsule/tablet formulation) and D (high fixed dose) with 19 subjects in each group, and with the exception of one, all subjects completed Phase B.

In Phase A, a total of 211 AEs were reported in 110 subjects including one orthostatic hypotension that led to hospitalization. Two subjects experienced severe AEs including hypotension and syncope in one, and dizziness and syncope in the other. Four subjects had a syncopal episode. The most frequent AEs included headache in 62%, dizziness in 17% and nausea in 13% of the subjects.

In Phase B, a total of 96 AEs were reported in 46 subjects. The incidence of any AE was highest in the highest dose (75/40 mg) group of BiDiL. In all treatment groups the most common AEs were headache and dizziness.

Severe AEs included severe headache in a subject in the highest dose group. Eleven subjects had hypotensive episodes, but none had a syncopal episode.