

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 20-727

Approved Labeling

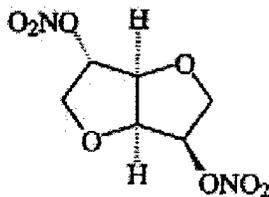
1 **BiDil[®]**
2 (isosorbide dinitrate and hydralazine hydrochloride)
3 **Tablets**

4 **DESCRIPTION**

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

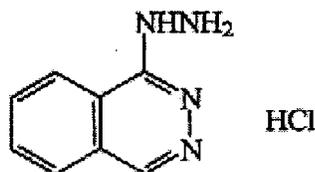
8 Isosorbide dinitrate is described chemically as 1,4:3,6-dianhydro-d-glucitol-2,5-dinitrate
9 and its structural formula is:

10



11
12 Isosorbide dinitrate is a white to off-white, crystalline powder with the empirical formula
13 C₆H₈N₂O₈ and a molecular weight of 236.14. It is freely soluble in organic solvents such
14 as alcohol, chloroform and ether, but is only sparingly soluble in water.

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



17
18 Hydralazine HCl is a white to off-white, crystalline powder with the empirical formula
19 C₈H₈N₄·HCl and a molecular weight of 196.64. It is soluble in water, slightly soluble in
20 alcohol, and very slightly soluble in ether.

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

23 The inactive ingredients in BiDil tablets include: anhydrous lactose, microcrystalline
24 cellulose, sodium starch glycolate, colloidal silicon dioxide, magnesium stearate,

25 hypromellose, FD&C Yellow No.6 aluminum lake, polyethylene glycol, titanium
26 dioxide, polysorbate 80.

27 CLINICAL PHARMACOLOGY

28 Mechanism of Action

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

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

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

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

42 Pharmacokinetics

43 *Hydralazine*

44 **Absorption and Distribution:** About 2/3 of a 50-mg dose of ¹⁴C-hydralazine HCl given
45 in gelatin capsules was absorbed in hypertensive subjects. In patients with heart failure,
46 mean absolute bioavailability of a single oral dose of hydralazine 75 mg varies from 10 to
47 26%, with the higher percentages in slow acetylators (See *Metabolism and Elimination*).
48 Administration of doses escalating from 75 mg to 1000 mg tid to congestive heart failure
49 patients resulted in an up to 9-fold increase in the dose normalized AUC, indicating non-
50 linear kinetics of hydralazine, probably reflecting saturable first pass metabolism.

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

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

60 After oral administration of hydralazine, the major circulating metabolites are
61 hydralazine pyruvate hydrazone and methyltriazolophthalazine. Hydralazine is the main

62 pharmacologically active entity; hydralazine pyruvate hydrazone has only minimal
63 hypotensive and tachycardic activity. The pharmacological activity of
64 methyltriazolophthalazine has not been determined. The major identified metabolite of
65 hydralazine excreted in urine is acetylhydrazinophthalazinone.

66 *Isosorbide Dinitrate*

67 **Absorption and Distribution:** Absorption of isosorbide dinitrate from tablets after oral
68 dosing is nearly complete. The average bioavailability of isosorbide dinitrate is about
69 25%, but is highly variable (10%-90%) due to first-pass metabolism and increases
70 progressively during chronic therapy. Serum concentrations reach their maximum about
71 one hour after ingestion.

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

74 Under steady-state conditions, isosorbide dinitrate accumulates significantly in muscle
75 (pectoral) and vein (saphenous) wall relative to simultaneous plasma concentrations.

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

84 Most isosorbide dinitrate is eliminated renally as conjugated metabolites.

85 *BiDil*

86 **Absorption and Bioavailability:** Following a single 75-mg oral dose of hydralazine plus
87 40 mg of isosorbide dinitrate to 19 healthy adults, peak plasma concentrations of
88 hydralazine (88 ng/mL/65 kg) and isosorbide dinitrate (76 ng/mL/65 kg) were reached in
89 1 hour. The half-lives were about 4 hours for hydralazine and about 2 hours for
90 isosorbide dinitrate. Peak plasma concentrations of the two active metabolites,
91 isosorbide-2-mononitrate and isosorbide-5-mononitrate, were 98 and 364 ng/mL/65 kg,
92 respectively, at about 2 hours. No information is currently available regarding the effect
93 of food on the bioavailability of hydralazine or isosorbide dinitrate from BiDil tablets.

94 **Special Populations**

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

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

99 **Renal Impairment:** The effect of renal impairment on the pharmacokinetics of
100 hydralazine has not been determined. In a study with 49 hypertensive patients on chronic

101 therapy with hydralazine in daily doses of 25-200 mg, the daily dose of hydralazine in 19
102 subjects with severely impaired renal function (creatinine clearance 5-28 mL/min) and in
103 17 subjects with normal renal function (creatinine clearance >100 mL/min) was not
104 different, suggesting no need for dose adjustment in patients with renal impairment. The
105 dialyzability of hydralazine has not been determined. In three studies, renal insufficiency
106 did not affect the pharmacokinetics of isosorbide dinitrate. Dialysis is not an effective
107 method for removing isosorbide dinitrate or its metabolite isosorbide-5-mononitrate from
108 the body.

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

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

115 No pharmacokinetic studies in special populations were conducted with BiDil.

116 **Pharmacokinetic Drug-Drug Interactions**

117 *Hydralazine*

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

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

127 In healthy males administered single oral doses of hydralazine 25 mg and either lisinopril
128 20 mg or enalapril 20 mg, C_{max} and AUC for lisinopril were each increased by about
129 30%, but enalapril concentrations were unaffected.

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

133 *Isosorbide Dinitrate*

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

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

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

143 *BiDil*

144 No pharmacokinetic drug-drug interaction studies were conducted with BiDil.

145 **Pharmacodynamics**

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

153 **Clinical Trials**

154 BiDil or a combination of isosorbide dinitrate and hydralazine hydrochloride was studied
155 in two placebo-controlled clinical trials in 1,692 patients with mild to severe heart failure
156 (mostly NYHA class II and III) and one active control trial (vs. enalapril) in 804 patients.

157 In the multicenter trial V-HeFT I, the combination of hydralazine and isosorbide dinitrate
158 75 mg/40 mg qid (n=186) was compared to placebo (n=273) in men with impaired
159 cardiac function and reduced exercise tolerance (primarily NYHA class II and III), and
160 on therapy with digitalis glycosides and diuretics. There was no overall significant
161 difference in mortality between the two treatment groups. There was, however, a trend
162 favoring hydralazine and isosorbide dinitrate, which on retrospective analysis, was
163 attributable to an effect in blacks (n=128). Survival in white patients (n=324) was similar
164 on placebo and the combination treatment.

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

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

175 The A-HeFT trial evaluated BiDil vs. placebo among 1,050 self-identified black patients
176 (over 95% NYHA class III) at 169 centers in the United States. All patients had stable
177 symptomatic heart failure. Patients were required to have LVEF \leq 35% or left ventricular
178 internal diastolic dimension $>$ 2.9 cm/m² plus LVEF $<$ 45%. Patients were maintained on

179 stable background therapy and randomized to BiDil (n=518) or placebo (n=532). BiDil
 180 was initiated at 20 mg isosorbide dinitrate/37.5 mg hydralazine hydrochloride three times
 181 daily and titrated to a target dose of 40/75 mg three times daily or to the maximum
 182 tolerated dose. Patients were treated for up to 18 months.

183 The randomized population was 60% male, 1% NYHA class II, 95% NYHA class III
 184 and 4% NYHA class IV, with a mean age of 57 years, and was generally treated with
 185 standard treatments for heart failure including diuretics (94%, almost all loop diuretics),
 186 beta-blockers (87%), angiotensin converting enzyme inhibitors (ACE-I; 78%),
 187 angiotensin II receptor blockers (ARBs; 28%), either ACE-I or ARB (93%), digitalis
 188 glycosides (62%) and aldosterone antagonists (39%).

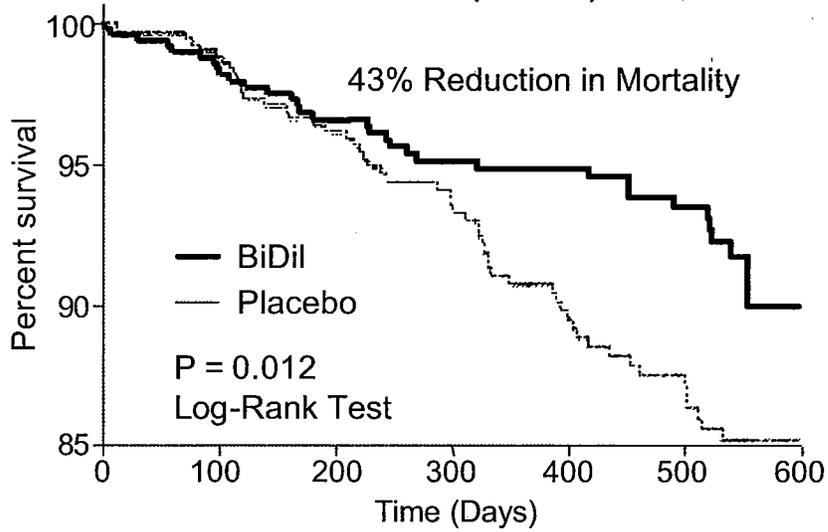
189 The primary end point was a composite score consisting of all-cause mortality, first
 190 hospitalization for heart failure, and responses to the Minnesota Living with Heart Failure
 191 questionnaire, with the individual components of the composite examined as separate
 192 endpoints. The trial was terminated early, at a mean follow-up of 12 months, primarily
 193 because of a statistically significant 43% reduction in all-cause mortality in the BiDil-
 194 treated group (p=0.012; see Table 1 and Figure 1). The primary endpoint was also
 195 statistically in favor of BiDil (p ≤ 0.021). The BiDil-treated group also showed a 39%
 196 reduction in the risk of a first hospitalization for heart failure (p<0.001; see Table 1 and
 197 Figure 2) and had statistically significant improvement in response to the Minnesota
 198 Living with Heart Failure questionnaire, a self-report of the patient's functional status, at
 199 most time points (see Figure 3). Patients in both treatment groups had mean baseline
 200 questionnaire scores of 51 (out of a possible 105).

201 Table 1. Results of A-HeFT (Intent-To-Treat Population)

End point	BiDil® N=518	Placebo N=532	Hazard Ratio (95% CI)	Risk Reduction with BiDil	P-value
Composite score	-0.16±1.93	-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

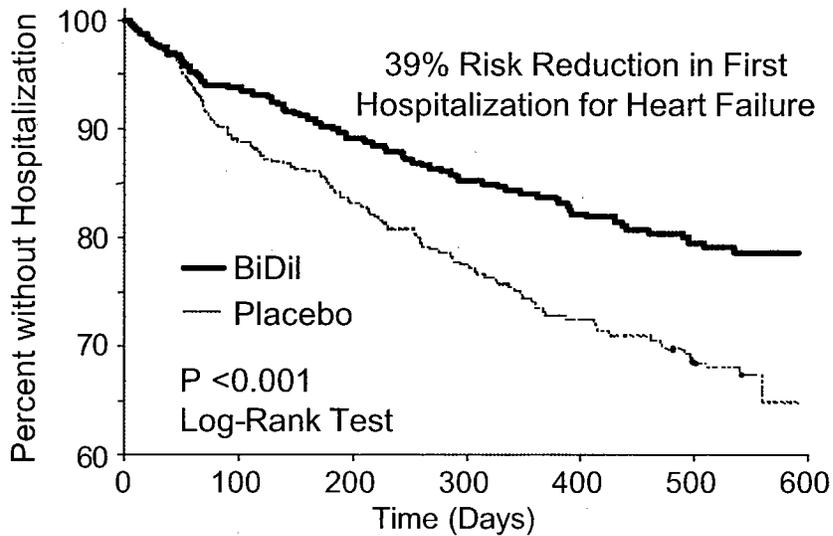
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203 **Figure 1: Kaplan-Meier Plot of Time to Death by All Cause**
 204 **in Black Patients (A-HeFT)**



215	BiDil, n = 518	463	407	360	314	253	16
216	Placebo, n = 532	466	401	340	285	233	25

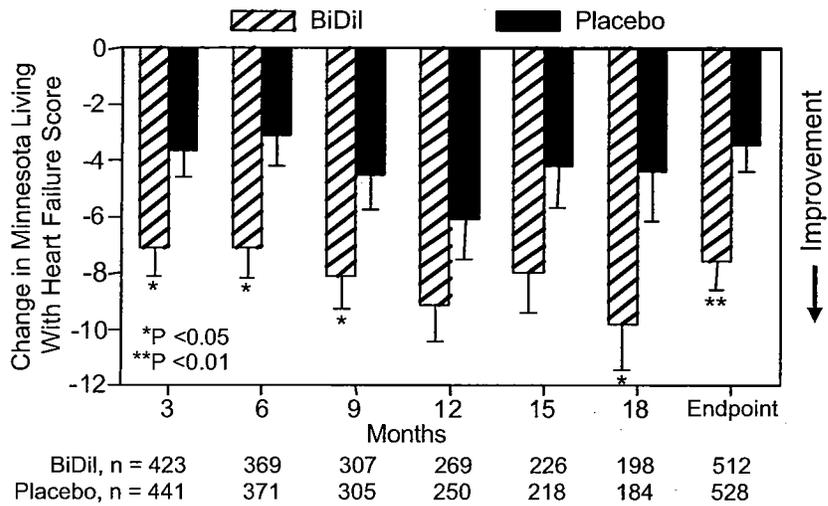
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 218
 219 **Figure 2: Kaplan-Meier Plot of Time to First Hospitalization**
 220 **for Heart Failure in Black Patients (A-HeFT)**



231	BiDil, n = 518	430	357	305	253	197	6
232	Placebo, n = 532	407	329	264	203	160	12

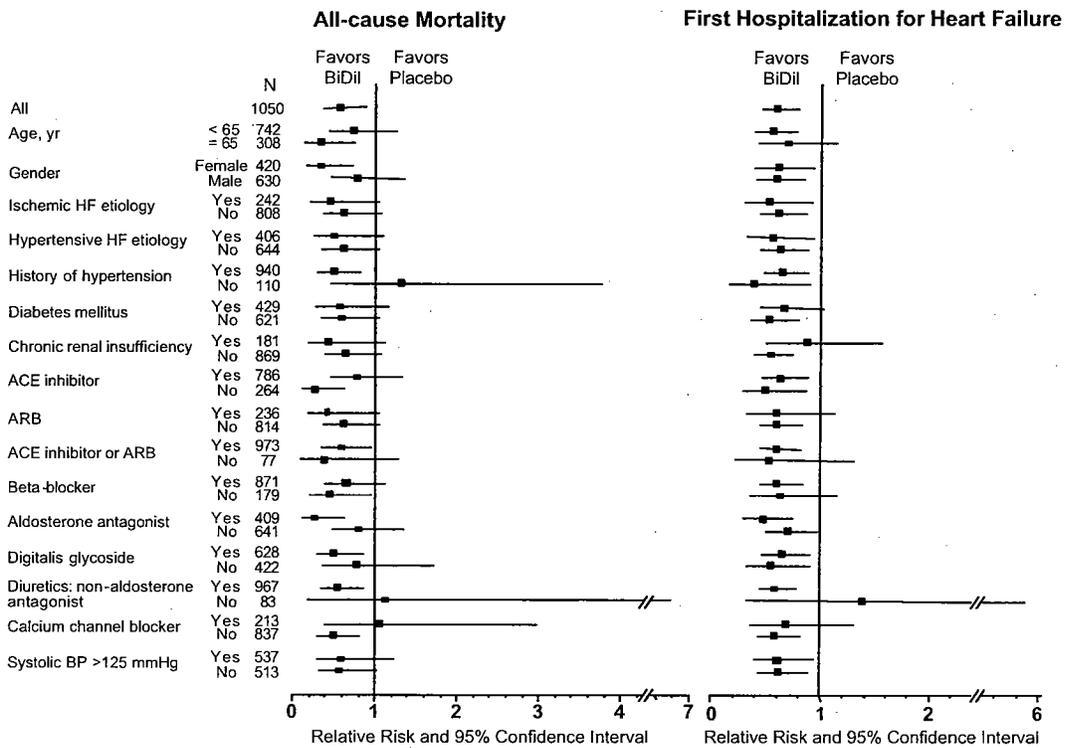
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Figure 3: Change in Minnesota Living with Heart Failure Score



Effects on survival and hospitalization 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 Characteristic Subgroups in Black Patients (A-HeFT)



267

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

275 **INDICATIONS AND USAGE**

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

283 **CONTRAINDICATIONS**

284 BiDil is contraindicated in patients who are allergic to organic nitrates.

285 **WARNINGS**

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

291 **PRECAUTIONS**

292 **General**

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

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

297 If systemic lupus erythematosus-like symptoms occur in patients treated with BiDil,
298 discontinuation of BiDil should be considered only after a thorough benefit-to-risk
299 assessment. Symptoms and signs of systemic lupus erythematosus usually regress when

300 hydralazine hydrochloride is discontinued but residua have been detected many years
301 later. Long-term treatment with steroids may be necessary. (See PRECAUTIONS.
302 Laboratory Tests.)

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

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

308 Careful clinical and hemodynamic monitoring is recommended when BiDil is
309 administered to patients with acute myocardial infarction to avoid the hazards of
310 hypotension and tachycardia.

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

314 Isosorbide dinitrate therapy may aggravate angina associated with hypertrophic
315 cardiomyopathy.

316 **Information for Patients**

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

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

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

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

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

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

337 **Laboratory Tests**

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

343 **Drug/Drug Interactions**

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

346 Patients treated with BiDil who receive any potent parenteral antihypertensive agent
347 should be continuously observed for several hours for excessive fall in blood pressure.

348 The effects of BiDil on vasodilators including alcohol may be additive.

349 Sildenafil: See WARNINGS.

350 Vardenafil: See WARNINGS.

351 Tadalafil: See WARNINGS.

352 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

353 *Hydralazine Hydrochloride*

354 An increased incidence of lung tumors (adenomas and adenocarcinomas) was observed in
355 a lifetime study in Swiss albino mice given hydralazine hydrochloride continuously in
356 their drinking water at a dosage of about 250 mg/kg per day (6 times the MRHD provided
357 by BiDil on a body surface area basis). In a 2-year carcinogenicity study of rats given
358 hydralazine hydrochloride by gavage at dose levels of 15, 30, and 60 mg/kg/day (up to 3
359 times the MRHD of BiDil on a body surface area basis), microscopic examination of the
360 liver revealed a small, but statistically significant increase in benign neoplastic nodules in
361 males (high-dosage) and females (both high and intermediate dosage groups). Benign
362 interstitial cell tumors of the testes were also significantly increased in the high-dose
363 group.

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

369 *Isosorbide Dinitrate*

370 No long-term animal studies have been performed to evaluate the mutagenic or
371 carcinogenic potential of isosorbide dinitrate. A modified two-litter reproduction study
372 among rats fed isosorbide dinitrate at 25 or 100 mg/kg/day (up to 9 times the Maximum

373 Recommended Human Dose of BiDil on a body surface area basis) revealed no evidence
374 of altered fertility or gestation.

375

376 **Pregnancy Category C**

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

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

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

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

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

399 **Nursing mothers**

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

404 **Pediatric use**

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

406 **Geriatric use**

407 Clinical studies of BiDil did not include sufficient numbers of subjects aged 65 and over
408 to determine whether they respond differently from younger subjects. Other reported

409 clinical experience has not identified differences in response between elderly and
 410 younger patients. In general, dose selection for an elderly patient should be cautious,
 411 usually starting at the low end of the dosing range, reflecting the greater frequency of
 412 decreased hepatic and renal function, and of concomitant disease or other drug therapies.
 413 Isosorbide dinitrate, its active metabolites, and hydralazine may be eliminated more
 414 slowly in elderly patients.

415 **ADVERSE REACTIONS**

416 *BiDil*

417 BiDil has been evaluated for safety in 517 heart failure patients in A-HeFT. A total of
 418 317 of these patients received BiDil for at least 6 months, and 220 received BiDil for at
 419 least 12 months. In A-HeFT, 21% of the patients discontinued BiDil for adverse
 420 experiences compared to 12% who discontinued placebo. Overall, adverse events were
 421 more common in BiDil-treated than in placebo-treated patients. Table 2 lists adverse
 422 events reported with an incidence of $\geq 2\%$ in patients treated with BiDil in A-HeFT, and,
 423 after rounding to the nearest 1%, occurring more frequently than in the placebo group,
 424 regardless of causality. Headache and dizziness were the two most frequent adverse
 425 events and were more than twice as frequent in the BiDil group. The most common
 426 reasons for discontinuing BiDil in the A-HeFT trial were headache (7%) and dizziness
 427 (4%).

428

429 Table 2. Adverse Events Occurring in the A-HeFT Study in $\geq 2\%$ of
 430 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
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431
432 The following adverse events were reported in A-HeFT in at least 1% but less than 2% of
433 patients treated with BiDil, and also occurred in at least 0.5% more patients than in
434 placebo-treated patients; all such events are included unless they are too non-specific to
435 be meaningful or appear to reflect underlying disease.

436 **Body as a Whole**: Allergic reaction, malaise.

437 **Central nervous system**: Somnolence.

438 **Gastrointestinal**: Cholecystitis.

439 **Metabolic**: Hypercholesteremia.

440 **Musculoskeletal**: Arthralgia, myalgia, tendon disorder.

441 **Skin**: Alopecia, angioedema, sweating.

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

446 *Prior experience with BiDil components*

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

449 **Digestive**: paralytic ileus.

450 **Cardiovascular**: paradoxical pressor response, crescendo angina.

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

453 **Genitourinary**: difficulty in urination.

454 **Hematologic**: blood dyscrasias, agranulocytosis, purpura, splenomegaly.

455 **Hypersensitive Reactions**: eosinophilia, hepatitis.

456 **Other**: nasal congestion, flushing, lacrimation, conjunctivitis.

457 **OVERDOSAGE**

458 There are no documented cases of overdosage with BiDil. The signs and symptoms of
459 overdosage with BiDil are expected to be those of excessive pharmacologic effect and
460 those that may occur with overdosage of either isosorbide dinitrate or hydralazine
461 hydrochloride administered alone.

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

463 **Signs and Symptoms**: The signs and symptoms of overdosage with BiDil are expected
464 to be those of excessive pharmacologic effect, i.e., vasodilatation, reduced cardiac output

465 and hypotension, and signs and symptoms include headache, confusion, tachycardia and
466 generalized skin flushing. Complications can include myocardial ischemia and
467 subsequent myocardial infarction, cardiac arrhythmia, and profound shock. Syncope,
468 coma and death may ensue without appropriate treatment.

469 **Treatment:** There is no specific antidote.

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

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

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

482 **Methemoglobinemia**

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

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

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

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

493 **DOSAGE AND ADMINISTRATION**

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

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

499 Although titration of BiDil can be rapid (3-5 days), some patients may experience side
500 effects and may take longer to reach their maximum tolerated dose. The dosage may be

501 decreased to as little as one-half BiDil Tablet 3 times a day if intolerable side effects
502 occur. Efforts should be made to titrate up as soon as side effects subside.

503 **HOW SUPPLIED**

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

507 **NDC 12948-001-12** bottle of 180.

508 **Keep bottles tightly closed.**

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

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

512 **Rx only**

513 Manufactured for:

514 NitroMed, Inc.

515 125 Spring Street

516 Lexington, MA 02421 USA

517 by

518 Schwarz Pharma Mfg., Inc.

519 P.O. Box 328

520 1101 C Avenue W.

521 Seymour, IN 47274 USA

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