National Formulary Review
Combination Isosorbide Dinitrate/Hydralazine (BiDil®)

VHA Pharmacy Benefits Management Strategic Health Care Group and the Medical Advisory Panel

Executive Summary

- **Indications:** BiDil® is a combination product containing isosorbide dinitrate (ISDN) and hydralazine, approved by the FDA as adjunct treatment to standard therapy for heart failure (HF) to improve survival, prolong time to hospitalization for HF, and improve patient-reported functional status in self-identified black patients.

- **Efficacy:** In the African-American Heart Failure Trial (A-HeFT), a controlled trial of 1050 self-identified black patients with New York Heart Association (NYHA) class III or IV HF, patients were randomized to treatment with the fixed-dose combination ISDN/hydralazine or placebo (in addition to standard therapy for HF). The treatment group was reported to experience a significant reduction in mortality (absolute risk reduction 4%, with a number needed to treat of 25 patients for the mean follow-up of 10 months) compared to patients in the placebo group (32 deaths or 6.2% vs. 54 deaths or 10.2%, respectively). Treatment was associated with a 43% improvement in survival (hazard ratio 0.57; p=0.01). There was also a 33% reduction in first hospitalization for HF with treatment compared to placebo (16.4% vs. 24.4%, respectively; p=0.001). The primary endpoint (based on a weighted composite score with a possible range -6 to +2, with a higher score representing a better outcome) was reported to be -0.1±1.9 in patients receiving the combination ISDN/hydralazine compared to -0.5±2.0 in the placebo group (p=0.01), indicating a benefit with ISDN/hydralazine in addition to standard drug therapy. The trial was planned for 18 months of follow-up but was terminated early.

- **Safety:** The most frequently reported adverse events in patients taking the fixed-dose combination ISDN/hydralazine in the A-HeFT trial were headache and dizziness, reported in twice as many patients compared to the placebo group. Discontinuations due to adverse events occurred in 21% of patients in the fixed-dose combination ISDN/hydralazine treatment group compared to 12% of patients receiving placebo. The combination ISDN/hydralazine should be used with caution in patients with volume depletion or who are hypotensive. Use of organic nitrates intermittently or chronically in any dosage form is contraindicated in patients receiving a phosphodiesterase inhibitor (e.g., sildenafil, tadalafil, vardenafil). Patients treated with hydralazine (a component of BiDil®) may develop symptoms similar to that of systemic lupus erythematosus. Drug discontinuation should be considered after evaluation of risk versus benefit of continuing therapy.

- **Dose:** The initial recommended dose of the fixed-dose combination ISDN 20 mg/hydralazine 37.5mg is one tablet three times daily. The dose may be titrated as tolerated to two tablets administered three times daily for a total daily dose of ISDN 120 mg/hydralazine 225 mg.

- **Cost:** The monthly drug cost for initial therapy with the fixed-dose combination of ISDN/hydralazine (BiDil®) in patients with advanced HF is approximately $115. The cost for maintenance therapy if increased to the recommended dose in A-HeFT (ISDN 120 mg/hydralazine 225 mg; two tablets three times daily) would be approximately $2765 per year. This compares to an annual cost of approximately $45 to $63 per patient per year if the patient were to receive a comparable dose of ISDN or isosorbide mononitrate (ISMN) and hydralazine as individual components of therapy, with an annual price difference of approximately $1340 per patient per year. Taking into consideration current utilization (regardless of race) of the agents as separate prescriptions, if 25% of the patients receiving combination therapy with hydralazine and a nitrate (as two prescriptions) were switched to the fixed-dose combination (BiDil®), the annual price increase would be approximately $4.2 million (considering only the price of the drug). This does not take into account the potential increase in use of combination therapy with a nitrate and hydralazine in patients with persistent symptoms on standard therapy for HF as per recent HF guideline recommendations. Adjunct therapy with the fixed-dose combination ISDN/hydralazine (BiDil®) has been reported to reduce costs and improve outcomes in a cost-effectiveness evaluation of HF related and all medical care costs treatment model of approximately one year; however, this model did not use generic nitrates and hydralazine as a comparator.

- **Recommendations:** It is recommended that the fixed-dose combination of ISDN/hydralazine (BiDil®) be available for nonformulary use in patients with HF, according to recommendations as specified in current national treatment guidelines, regardless of race. As the fixed-dose combination does not offer a cost advantage or in most cases, a decrease in the number of times per day the dose is administered (and in a few instances may result in the patient needing to taking more pills per day with the fixed-dose combination product), as compared to the agents prescribed separately, the fixed-dose combination should be reserved for those patients with advanced HF where the clinician has determined that the patient is having difficulty adhering to the medication regimen due to the number of pills per day, and that switching to the fixed-dose combination product would decrease the pill burden and improve adherence. For patients where the clinician is considering initiating therapy with a combination of a nitrate and hydralazine (per clinical practice guideline recommendations), it is recommended that the two medications be prescribed separately, and adherence monitored in the patient, before considering the fixed-dose combination product.

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Introduction[1-11]

Combination isosorbide dinitrate (ISDN)/hydralazine (BiDil®, NitroMed, Inc) received FDA approval for marketing in the U.S. on June 23, 2005. The fixed-dose combination product is indicated for adjunct treatment to standard therapy for heart failure (HF) to improve survival, prolong time to hospitalization for HF, and improve patient-reported functional status in self-identified black patients.[1] The majority of patients in the clinical trial that led to approval of this product were receiving standard therapy with a loop diuretic, an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin II receptor antagonist, and a beta-adrenergic blocker. Many patients were also taking a cardiac glycoside or an aldosterone antagonist.

For patients with Stage C HF (structural heart disease with prior or current symptoms), current clinical practice guideline recommendations are to consider the combination of hydralazine and a nitrate in patients who are receiving therapy with an ACEI and a beta-adrenergic blocker, but who are continuing to experience symptoms.[2] In addition, treatment with the combination of hydralazine and a nitrate is considered reasonable in patients with HF who are unable to take an ACEI or angiotensin II receptor antagonist due to intolerance, hypotension, or renal insufficiency.[2]

Studies that specifically address the efficacy of the combination of hydralazine and a nitrate in patients with HF who cannot tolerate ACEIs have not been conducted. The first Vasodilator-Heart Failure Trial (V-HeFT I) reported a 34% reduction in mortality by two years in veteran patients with HF treated with the combination of hydralazine and ISDN (prescribed separately) compared to placebo.[3] In V-HeFT II, that enrolled veteran patients with New York Heart Association (NYHA) class II or III HF, the mortality rate was lower with enalapril at 18% compared to 25% in patients receiving combination therapy with ISDN and hydralazine.[4]

The possibility of racial differences in response to therapy was initially reported in a subanalysis of patients enrolled in the SOLVD Treatment Trial. Patients with mild to moderate HF who received enalapril had a significant decrease of 16% in all-cause mortality and a 26% decreased risk of death or hospitalizations for HF compared to patients on placebo.[5] When matched cohorts of white patients were compared to black patients on an ACEI enrolled in this trial, white patients experienced a decreased risk for hospitalizations due to HF which was not seen in the cohort of black patients.[6]

Racial differences in response to therapy have also been reported in subanalyses of the V-HeFT I and V-HeFT II trials. The annual mortality rate was lower in black patients receiving hydralazine and ISDN in V-HeFT I compared to black patients receiving placebo (9.7% vs. 17.3%, respectively; P=0.04); a similar effect was not seen in white patients on hydralazine and ISDN vs. placebo (annual mortality rate 16.9% vs. 18.8%, respectively).[7] In V-HeFT II, white patients on enalapril experienced a decrease in mortality compared to treatment with hydralazine and ISDN (annual mortality rate 11.0% vs. 14.9%, respectively; P=0.02), whereas black patients did not have a similar benefit (annual mortality rate with enalapril 12.8% vs. 12.9% with hydralazine and ISDN).[7] In summary, this information suggests that black patients with HF experience a similar reduction in mortality with the combination of hydralazine and ISDN as with enalapril, and a decrease in mortality with the combination of hydralazine and ISDN compared to placebo. Whereas white patients experience a reduction in mortality with enalapril over that of the combination of hydralazine and ISDN, but not with the combination of hydralazine and ISDN compared to placebo.

Based on a pooled relative risk analysis conducted by the U.S. Department of Health and Human Services, there was no evidence that mortality differed substantially by race in patients treated with an ACEI, with an estimate for white patients of 0.89 (95% CI 0.82-0.97) and 0.89 (85% CI 0.74-1.06) for black patients.[8] The question of whether there is a difference in benefit with the beta-adrenergic blockers in patients with HF based on race has also been raised based on conflicting results of subanalyses of black patients.[9,10] However, the U.S. Department of Health and Human Services reported the estimate of pooled random-effects of the relative risk for mortality in black patients

receiving a beta-adrenergic blocker (i.e., bisoprolol, carvedilol, or metoprolol) to be 0.67 (95% CI 0.39-1.16) compared to 0.63 (95% CI 0.52-0.77) for white patients.[8]

To substantiate the efficacy of combination hydralazine and ISDN in black patients with HF, a prospective randomized controlled trial, the African-American Heart Failure Trial or A-HeFT, was undertaken. Results of this trial reported that the fixed-dose combination of ISDN and hydralazine increased survival and reduced the rate of first hospitalization for HF in black patients with advanced HF receiving standard therapy compared to placebo[11] (refer to clinical trial results in the following sections: Efficacy Measures, Clinical Trial Data, and Appendix 1).

Pharmacology[1,11]

Peripheral vasodilators can produce favorable hemodynamic effects in patients with HF. Both ISDN and hydralazine are vasodilators, with ISDN acting as an arterial and venous vasodilator, and hydralazine being primarily an arterial vasodilator.

Due to the differing results with neurohormonal treatment for HF based on race, it has been suggested that an alternative mechanism exists for influencing the progression of HF in black patients.[11] As nitric oxide may protect against myocardial and vascular remodeling, and endothelial function and bioavailability of nitric oxide may not be optimal in black patients, it has been proposed that ISDN may act as a nitric oxide donor, with hydralazine potentially inhibiting the degradation of and enhancing the effects of nitric oxide.[11]

FDA Approved Indication(s) and Unlabeled Uses[1,12]

Combination ISDN/hydralazine (BiDil®, NitroMed, Inc) received FDA approval for marketing in the U.S. on June 23, 2005. The combination product is indicated as adjunct treatment to standard therapy for HF to improve survival, prolong time to hospitalization for HF, and improve patient-reported functional status in self-identified black patients.[1]

Approved uses for the individual components of BiDil® include the following: ISDN is approved for the treatment and prevention of angina; hydralazine is indicated for treatment of essential hypertension. An unlabeled use of ISDN is for the treatment of congestive HF (in combination with cardiac glycosides and diuretics or with hydralazine); an unlabeled use for hydralazine (in combination with cardiac glycosides, diuretics, and/or other vasodilators) also includes the treatment of patients with congestive HF.[12]

Dosage and Administration[1,4,11]

Availability	Initial Dose	Maximum Dose	Comments
ISDN 20 mg/ hydralazine 37.5 mg tablets	One tablet (20 mg/37.5 mg) three times daily	Two tablets administered three times daily (ISDN 120 mg/hydralazine 225 mg total daily dose)	May decrease to ½ tablet three times daily if intolerable side effects; consider retitration if side effects resolve

In A-HeFT, the mean number of tablets per day in the treatment group was 3.8±2.5 and 4.7±2.2 in the placebo group; with 68% of patients in the treatment group achieving the target dose of two tablets three times daily, compared to 88.9% in the placebo group.[11] Patients receiving ISDN and hydralazine in combination in V-HeFT II received an average of ISDN 100mg and hydralazine 200mg daily.[4]

Adverse Events[1]

The most frequently reported adverse events in patients taking the fixed-dose combination ISDN/hydralazine in A-HeFT were headache and dizziness, taking place in twice as many patients compared to the placebo group. Discontinuations due to adverse events occurred in 21% of patients in the treatment group compared to 12% of patients receiving placebo. Adverse events reported in A-HeFT are shown below.

Adverse Event[a]	ISDN/hydralazine, % (n=517)	Placebo, % (n=527)
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
DC due to AE	21	12

[a]Adverse events occurring in ≥ 2% of patients receiving treatment with the fixed-dose combination ISDN/hydralazine, and more frequently in the treatment group

Look-alike/Sound-alike Error Risk Potential

As part of a pilot program, the VA PBM and Center for Medication Safety queried a multi-attribute drug product search engine for similar sounding and appearing drug names based on orthographic and phonological similarities, as well as similarities in dosage form, strength and route of administration. By incorporating similarity scores as well as clinical judgment, it was determined that the following drug names may pose as potential sources of drug name confusion.

Drug Name	Potential Name Confusion	Potential Severity	Probability	SAC[a]
Isosorbide dinitrate/ Hydralazine (generic)	Isordil	Minor	Occasional	1
	Isosorbide dinitrate	Minor	Occasional	1
	Hydralazine	Minor	Occasional	1
	Hydroxyzine	Moderate	Uncommon	1
BiDil (brand)	Bentyl	Moderate	Remote	1
	Isordil	Minor	Uncommon	1
	Paxil	Minor	Remote	1
	Plendil	Minor	Remote	1

[a] SAC=Safety Assessment Code (3=highest risk; 2=intermediate risk; 1=lowest risk)

Contraindications/Warnings/Precautions[1]

The combination ISDN/hydralazine should be used with caution in patients with volume depletion or who are hypotensive. Precautions for BiDil® include those precautions listed for isosorbide dinitrate and for hydralazine. Patients receiving a phosphodiesterase inhibitor should not be prescribed BiDil® due to the drug interaction between this class and nitrates (see Drug Interactions below). Patients treated with hydralazine (a component of BiDil®) may develop symptoms similar to that of systemic lupus erythematosus. Drug discontinuation should be considered after evaluation of risk versus benefit of continuing therapy.

Drug Interactions[1]

Use of organic nitrates intermittently or chronically in any dosage form is contraindicated in patients receiving a phosphodiesterase inhibitor (e.g., sildenafil, tadalafil, vardenafil).

Single dose administration of hydralazine with a beta-adrenergic blocker (metoprolol, propranolol) or an ACEI (e.g., lisinopril) resulted in an increase in Cmax and AUC of the beta-adrenergic blocker and ACEI. Monoamine oxidase inhibitors in conjunction with BiDil® (due to the hydralazine component of the combination) should be used with caution due to the synergistic effect resulting in significant blood pressure reduction.
No pharmacokinetic drug interaction studies have been conducted with BiDil®.

Efficacy Measures

The efficacy measures relating to the effect of the fixed-dose combination ISDN/hydralazine on morbidity and mortality in patients with HF in one randomized, placebo-controlled trial (A-HeFT)[11] are included below:

Primary endpoint
- Primary composite endpoint score (see below)

Endpoint	Score
Death	-3
Survival	0
1st HF hospitalization	-1
No hospitalization	0
Quality of Life	
Improved ≥ 10	+2
Improved 5-9	+1
Change < 5	0
Worsened 5-9	-1
Worsened ≥ 10	-2
Possible score	-6 to +2

Secondary endpoints
- All-cause death
- First hospitalization for HF
- Change in Quality of Life (QOL) score (at 6 months)

Clinical Trial Data[3,4,11]

Morbidity and mortality (RCTs): One publication of a randomized, double-blind, placebo-controlled trial in self-identified black patients with advanced HF (NYHA class III to IV) using the fixed-dose combination of ISDN/hydralazine was identified[11] and is discussed below (details of the trial can be found in Appendix 1).

In A-HeFT,[11] 1050 patients were randomized to receive either ISDN/hydralazine at an initial dose of one tablet ISDN 20 mg/hydralazine 37.5 mg three times daily, and titrated as tolerated to two tablets three times daily for a total daily dose of ISDN 120 mg/hydralazine 225 mg, or placebo. The mean number of tablets per day in the treatment group was 3.8±2.5 and 4.7±2.2 in the placebo group; with 68% of patients in the treatment group achieving target dose compared to 88.9% in the placebo group. The trial was planned for 18 months of follow-up but was terminated early (mean follow-up 10 months) due to a significant reduction in mortality in patients receiving treatment (32 deaths/518 patients; 6.2%) compared to those on placebo (54 deaths/532 patients; 10.2%). Treatment was associated with a 43% improvement in survival (hazard ratio 0.57; p=0.01). There was also a 33% reduction in first hospitalization for HF (another pre-specified component of the primary endpoint) with treatment compared to placebo (16.4% vs. 24.4%, respectively; p=0.001). The primary endpoint was a composite score (possible range -6 to +2, with a higher score representing a better outcome) with weighted values based on mortality, survival to the

end of the trial, first hospitalization for HF, no hospitalizations, and change in QOL. It was reported that patients receiving the combination ISDN/hydralazine had a primary composite score of -0.1±1.9 compared to -0.5±2.0 in the placebo group (p=0.01), indicating a benefit with ISDN/hydralazine in addition to standard drug therapy.[11]

As mentioned in the Introduction, there have also been two trials using combination therapy of ISDN and hydralazine in patients with chronic HF, administered as their individual components. In V-HeFT I 642 veteran men with symptomatic HF, receiving digoxin and a diuretic, were randomized to treatment with prazosin, a nitrate plus hydralazine, or placebo. The dose of ISDN was 20 mg four times daily, increased to two doses four times daily for a total daily dose of 160 mg; while hydralazine was initiated at 37.5 mg four times daily, titrated to two doses four times daily for a total daily dose of 300 mg. The mean daily dose for ISDN in V-HeFT I was 136 mg and for hydralazine was 270 mg. It was reported that treatment with the combination of ISDN and hydralazine reduced mortality by two years compared to placebo (relative risk reduction 34%, CI 0.04 to 0.54, p<0.028).[3]

In V-HeFT II, treatment with ISDN and hydralazine (target doses the same as in V-HeFT I) was compared to enalapril (target dose 20 mg daily) in 804 veteran men with chronic congestive HF (majority NYHA class II and III HF) who were receiving treatment with digoxin and a diuretic. The average daily dose for ISDN was 100 mg, and 199 mg for hydralazine, compared to 15 mg for enalapril. The mortality rate was 18% in patients treated with enalapril compared to 25% in patients receiving combination therapy with hydralazine and ISDN (risk reduction 28.2%, p=0.016).[4] The authors concluded that the similar reduction in mortality seen with the combination of ISDN and hydralazine in V-HeFT I and V-HeFT II, compared with the mortality in the placebo group, along with the reduction in mortality seen with an ACEI, suggested that there is benefit in using a vasodilator as part of the treatment regimen in patients with HF, and that there may be an additional benefit of using the two treatments together.[4]

Acquisition Cost

Drug	Price/ Tablet	Annual Price Per Patient[a]	Annual Price Per Patient[b]
ISDN 20mg/hydralazine 37.5 mg (BiDil®)	$1.28	$1382.40 (ISDN 60 mg/ hydralazine 112.5 mg per day)	$2764.80 (ISDN 120 mg/ hydralazine 225 mg per day)

[a] One tablet three times daily
[b] Two tablets three times daily

Cost Comparison

Drug[a]	Price/Tablet	Daily Regimen	Total Daily Dose	Annual Price/Patient
ISDN 20 mg	$0.0073	1 tablet three times daily	60 mg	$7.88
ISDN 20 mg	$0.0073	2 tablets three times daily	120 mg	$15.77
ISMN 60 mg	$0.0383	1 tablet daily	60 mg	$13.79
ISMN 120 mg	$0.0664	1 tablet daily	120 mg	$23.90
Hydralazine 25 mg	$0.0260	1 tablet three times daily	75 mg	$28.08
Hydralazine 25 mg	$0.0260	1 tablet four times daily	100 mg	$37.44
Hydralazine 50 mg	$0.0326	1 tablet three times daily	150 mg	$35.21
Hydralazine 50 mg	$0.0326	1 tablet four times daily	200 mg	$46.94

[a] ISMN=Isosorbide mononitrate

VA Utilization FY2005 (Based on 12,626 Patients on Nitrates and Hydralazine)

Drug	Percent Utilization[a]	Average Daily Dose	Annual Price/Patient	Estimated Annual Price Increase Per Patient if Switched to BiDil
ISDN	48.4%	65.2 mg	$8.56	ISDN + hydralazine vs. BiDil: ↑ $1346.31 ISMN + hydralazine vs. BiDil: ↑ $1341.61
ISMN	44.4%	57.7 mg	$13.26	
Hydralazine	100%	117.3 mg	$27.53	

[a] utilization of nitroglycerin products not shown due to low percentage (1.4%)

Cost-Effectiveness Analysis[13]

Results of a cost-effectiveness analysis, supported by the manufacturer of BiDil®, was conducted using resource utilization and outcome data from A-HeFT. The evaluation compared the cost of treatment with the fixed-dose combination ISDN/hydralazine product (BiDil®) vs. placebo. The Medicare database was used for cost estimates. The manufacturer's announced price of $1.80 per tablet for BiDil® was used, along with the average daily dose and adherence as was reported in A-HeFT, for calculating medication costs resulting in an average cost per day of $6.38. It was reported that patients receiving treatment with the fixed-dose combination ISDN/hydralazine experienced a 41% decrease in HF related hospitalization days. When the cost of the fixed-dose combination ISDN/hydralazine was included in the calculations for resource utilization, HF related costs were 6% lower with a cost savings of $533 (95% CI $2422 savings to $2241 expenditures; p=0.36). Using bootstrap scatterplots of within-trial cost-effectiveness, treatment with fixed-dose combination ISDN/hydralazine was dominant (i.e., saved lives and reduced costs) in 49% of the simulations for HF related care, and in 71% of the simulations for all medical care. For HF related care, the cost of therapy was less than $10,000 per life-year in 66% of the simulations and less than $50,000 per life-year in 92% of the simulations. When evaluating all medical care, the cost of therapy was less than $10,000 per life-year in 82% of the simulations and less than $50,000 per life-year in 95% of the simulations. By extending the time horizon past the length of the trial (i.e., greater than 12 months per the cost-effectiveness evaluation), the HF related cost-effectiveness for treatment with the fixed-dose combination ISDN/hydralazine was calculated to be $16,600 per life-year gained at one additional year, and a lifetime case estimate of $41,800 per life-year gained; assuming that the benefit of therapy did not extend beyond that of the trial duration. Assuming that the benefit was extended for one year in addition to the trial duration, the lifetime case estimate would then be $22,900 per life-year gained for HF related costs, and $32,900 per life-year gained for all medical care. Results of the sensitivity analysis reported that incremental costs were influenced most by changes in hospitalization costs and the price of the fixed-dose combination ISDN/hydralazine. For HF related costs, treatment with the fixed-dose combination ISDN/hydralazine was dominant up to a daily cost of $8.05 per patient; with a daily cost up to $12.00 per patient being dominant for all medical care. Above these daily treatment costs for the fixed-dose combination ISDN/hydralazine, the within-trial cost-effectiveness ratios increased by $6400 per life-year for each $1 increase in drug cost per patient per day. Subgroup analysis of incremental cost-effectiveness ratios showed that treatment was dominant for patients not receiving an ACEI at baseline and for those not on a beta-adrenergic blocker at baseline, although the percent of patients in these subgroups was low (e.g., 25% and 13%, respectively). Treatment was also dominant for those patients receiving intense concomitant therapy (i.e., combination therapy with an ACEI or angiotensin II receptor antagonist, a beta-adrenergic blocker, digoxin, and spironolactone).[13]

It should be noted that this cost-effectiveness analysis was conducted comparing the fixed-dose combination product to placebo, not the generic ISDN (or ISMN) and hydralazine given as two prescriptions (which is current practice in the VA), and did not take into account the benefit seen with ISDN and hydralazine in the V-HeFT trials.

According to current VA price information for the fixed-dose combination ISDN/hydralazine product (BiDil®), the annual price per patient ranges from approximately $1382 for 1 tablet three times daily to $2765 for 2 tablets three times daily. Comparable doses for either ISDN or ISMN prescribed in combination with hydralazine range in price from approximately $45 to $63 per patient per year. Depending on the dose and whether ISDN or ISMN are prescribed, the number of tablets prescribed per day could be either more, less, or equal to that of the fixed-dose combination. Based on current VA utilization of 12,626 patients (regardless of race) receiving combination therapy with hydralazine and a nitrate (as two prescriptions; not specific to HF diagnosis), the annual price increase per patient would be approximately $1340 if switched to the fixed-dose combination (BiDil®). This would be an increase of ~$4.2 million per year (considering only the price of drug), if 25% of the patients currently prescribed combination therapy were switched to the fixed-dose combination. This does not take into account that these patients, if on the combination of a nitrate and hydralazine for HF, were most likely prescribed the combination if they were unable to take an ACEI, as per previous HF guideline recommendations. As more recent HF guidelines also recommend the combination of a nitrate and hydralazine in patients with persistent symptoms on standard therapy with an ACEI and beta-adrenergic blocker, it is anticipated that there would be an increase in utilization of this therapy, with the potential for a larger impact on cost than estimated above if the fixed-dose combination were used instead of the two agents prescribed separately.

Data Compilation Table

Component of Primary Endpoint	All-Cause Death
Results: ISDN/hydralazine	32/518 (6.2%)
Results: Placebo	54/532 (10.2%)
Treatment duration	10 months (mean)
Relative Risk Reduction	39%
Absolute Risk Reduction (95% CI)	4% (0.7 to 7.3)
NNT (95% CI)	25 (14 to 143)

Conclusions

The fixed-dose combination of ISDN/hydralazine has been reported to statistically significantly reduce mortality and risk for first HF hospitalization in self-identified black patients with HF (majority NYHA class III) on standard therapy in one randomized, placebo-controlled trial. Adjunct therapy with the fixed-dose combination ISDN/hydralazine (BiDil®) has been reported to reduce costs and improve outcomes in a cost-effectiveness evaluation of HF related and all medical care costs treatment model of approximately one year, but only compared to placebo and not the generic formulations of ISDN and hydralazine.

As a fixed-dose combination product of ISDN and hydralazine was used in A-HeFT (not the individual components of ISDN, or ISMN and hydralazine given as two prescriptions, as typically prescribed in the VA), dose equivalencies for ISMN are an estimate of those used in the trial. The individual components of ISDN and hydralazine in combination have been studied in patients with HF and reported to reduce mortality compared to placebo. A similar mortality rate was found in patients treated with the combination of hydralazine and ISDN in another trial, but this trial compared treatment with ISDN and hydralazine to treatment with an ACEI, with a lower mortality reported in patients treated with an ACEI. When the results of these trials were analyzed based on race, there was a lower rate of mortality in black patients receiving hydralazine and ISDN compared to black patients receiving placebo; but this benefit was not evident in white patients on hydralazine and ISDN. In addition, white patients on the ACEI experienced a decrease in mortality compared to treatment with hydralazine and ISDN, whereas black patients did not have a similar benefit.

Clinical practice guidelines recommend that combination of a nitrate and hydralazine may be considered in patients with HF who 1) are unable to take an ACEI or angiotensin II receptor antagonist due to intolerance, hypotension, or renal insufficiency, or 2) are receiving therapy with an ACEI and a beta-adrenergic blocker, but who are continuing to experience symptoms. These recommendations for use are not based on the race of the patient, although it is stated that the benefits reported in A-HeFT have not been evaluated in other patient populations.

Recommendations

It is recommended that the fixed-dose combination of ISDN/hydralazine be available for nonformulary use in patients with HF according to recommendations as specified in current national treatment guidelines (i.e., patients who are unable to take an ACEI or angiotensin II receptor antagonist due to intolerance, hypotension, or renal insufficiency; or patients who are receiving therapy with an ACEI and a beta-adrenergic blocker, but are continuing to experience symptoms), regardless of race. As the fixed-dose combination does not offer a cost advantage and, in some cases, may result in the patient needing to take more pills per day compared to the agents prescribed separately, the fixed-dose combination should be reserved for those patients with advanced HF where the clinician has determined that the patient is having difficulty adhering to the medication regimen due to the number of pills per day, and that switching to the fixed-dose combination would decrease the pill burden and significantly improve adherence. For patients where the clinician is considering initiating therapy with a combination of a nitrate and hydralazine (per clinical practice guideline recommendations), it is recommended that the two medications be

prescribed separately, and adherence monitored in the patient, before considering the fixed-dose combination product.

References

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Appendix 1: Evidence Table (A-HeFT)

<table>
<tr><th>Trial</th><th>Inclusion/Exclusion/Endpoints</th><th>Treatment/Endpoint Score</th><th>Baseline/Results</th><th>Adverse Events</th></tr>
<tr>
<td>A-HeFT 2004[11]

MC, R, DB, PC

U.S.</td>
<td><u>Inclusion criteria</u>
18 yrs of age or older, self-identified as black (African descent), NYHA class III or IV X ≥ 3 months, LVD within 6 months (LVEF ≤ 35% or ≤ 45%with LV internal end-diastolic diameter > 2.9 cm/m^2 BSA or > 6.5 cm by ECHO); variation in body weight < 2.5% in 2 wks prior to randomization

<u>Exclusion criteria</u>
Pregnant or nursing women or of child-bearing age w/o contraception; AMI, ACS, or stroke within 3 months; cardiac surgery or PCI within 3 months or potential for during study; valvular heart disease, hypertrophic or restrictive cardiomyopathy, active myocarditis, uncontrolled HTN; history cardiac arrest or life-threatening arrhythmias within 3 months (unless ICD); IV inotropes within 1 month; potential for cardiac transplant; symptomatic hypotension; terminal illness other than HF; unable to complete QOL questionnaire; contraindications to nitrates or hydralazine

<u>Endpoints</u>
Primary: composite score (weighted values for all-cause mortality, 1st HF hosp during 18 months, change in QOL by MLHF at 6 months)
Secondary: components of primary endpoint, CV death, total HF hosp, total HF hosp days, overall QOL, unscheduled ER or OP visits, change B-type natriuretic peptide at 6 months, need for cardiac transplant, and change LVEF, LV diastolic dimension, and LV wall thickness at 6 months</td>
<td>Standard therapy for HF (determined by provider) e.g., ACEIs, ARBs, beta-blockers, X ≥ 3 months, digoxin, spironolactone, and diuretics

<u>Treatment phase</u>
Randomized to placebo or combination ISDN/hydralazine 20 mg/37.5 mg one tablet three times daily; if no drug-related AEs, dose increased to two tablets three times daily (total daily dose ISDN/hydralazine 120 mg/225 mg)

<table>
<tr><th>Endpoint</th><th>Score</th></tr>
<tr><td>Death</td><td>-3</td></tr>
<tr><td>Survival</td><td>0</td></tr>
<tr><td>1st HF hosp</td><td>-1</td></tr>
<tr><td>No hosp</td><td>0</td></tr>
<tr><td>QOL</td><td></td></tr>
<tr><td>Improved ≥ 10</td><td>+2</td></tr>
<tr><td>Improved 5-9</td><td>+1</td></tr>
<tr><td>Change < 5</td><td>0</td></tr>
<tr><td>Worsened 5-9</td><td>-1</td></tr>
<tr><td>Worsened ≥ 10</td><td>-2</td></tr>
<tr><td>Possible</td><td>-6 to +2</td></tr>
</table>
</td>
<td>
<table>
<tr><th>Baseline</th><th>Treatment</th><th>Placebo</th></tr>
<tr><td>Age (yrs)</td><td>56.7±12.7</td><td>56.9±13.3</td></tr>
<tr><td>Male</td><td>55.8%*</td><td>63.9%</td></tr>
<tr><td>NYHA III</td><td>96.7%</td><td>94.7%</td></tr>
<tr><td>DM</td><td>44.8%*</td><td>37.0%</td></tr>
<tr><td>LVEF</td><td>23.9±7.3%</td><td>24.2±7.5%</td></tr>
<tr><td>DBP</td><td>77.6±10.3*</td><td>75.6±10.5</td></tr>
<tr><td>MLHF</td><td>50.9±24.9*</td><td>50.7±25.5</td></tr>
<tr><td>ACEI</td><td>69.4%</td><td>69.5%</td></tr>
<tr><td>ARB</td><td>17.2%</td><td>16.5%</td></tr>
<tr><td>BB</td><td>74.1%</td><td>73.5%</td></tr>
<tr><td>Carvedilol</td><td>55.2%</td><td>55.8%</td></tr>
<tr><td>Spironolactone</td><td>40.2%</td><td>37.6%</td></tr>
</table>
* statistically significant difference vs. placebo

<u>Mean follow-up</u>: 10 months (study terminated early due to significant difference in mortality)

<u>Survival</u>: Significant 43% improvement in survival (HR 0.57; p=0.01)

<u>Target dose</u>: Treatment group (68%) vs. placebo (88.9%); p<0.001

<u>Mean number tablets/day</u>: Treatment group (3.8±2.5) vs. placebo (4.7±2.2); p<0.001

<table>
<tr><th>Endpoint</th><th>Treatment (N=518)</th><th>Placebo (N=532)</th><th>p value</th></tr>
<tr><td>Primary (score)</td><td>-0.1±1.9</td><td>-0.5±2.0</td><td>0.01</td></tr>
<tr><td>All-cause death</td><td>32 (6.2%)</td><td>54 (10.2%)</td><td>0.02</td></tr>
<tr><td>1st HF hosp</td><td>85 (16.4%)</td><td>130 (24.4%)</td><td>0.001</td></tr>
<tr><td>Change QOL*</td><td>-5.6±20.6</td><td>-2.7±21.2</td><td>0.02</td></tr>
</table>
* lower score reflects better QOL
</td>
<td>
<table>
<tr><th>AE</th><th>Treatment</th><th>Placebo</th></tr>
<tr><td>HF exacerbation</td><td>8.7%*</td><td>12.8%</td></tr>
<tr><td>Severe HF exacerbation</td><td>3.1%*</td><td>7.0%</td></tr>
<tr><td>Headache</td><td>47.5%</td><td>19.2%**</td></tr>
<tr><td>Dizziness</td><td>29.3%</td><td>12.3%**</td></tr>
</table>
* statistically significant difference vs. placebo
** statistically significant difference vs. treatment
</td>
</tr>
<tr><td colspan="5">Study Conclusions
• Treatment with combination ISDN/hydralazine, in addition to standard therapy for HF, improves survival and decreases the rate of first hospitalizations for HF in self-identified black patients with NYHA class III to IV HF.</td></tr>
<tr><td colspan="5">Quality Assessment (Fair)
• Significant differences in baseline characteristics
• Intention to treat analysis
• Stratified according to background beta-blocker treatment
• Primary endpoint based on weighted score used to increase the statistical power of detecting the endpoint in a patient population of moderate size</td></tr>
</table>

ACEI=angiotensin-converting enzyme inhibitor; ACS=acute coronary syndrome; AE=adverse event; AMI=acute myocardial infarction; ARB=angiotensin II receptor antagonist; ARR=absolute risk reduction; BB=beta-blocker; BSA=body surface area; DB=double-blind; ECHO=echocardiography; ER=emergency room; HF=heart failure; Hosp=hospitalization; HTN=hypertension; ICD=implantable cardiac defibrillator; ISDN=isosorbide dinitrate; IV=intravenous; LV=left ventricular; LVD=left ventricular dysfunction; LVEF=left ventricular ejection fraction; MC=multicenter; MLHF=Minnesota Living with Heart Failure questionnaire; N=number of patients; NYHA=New York Heart Association; OP=outpatient; PC=placebo-controlled; PCI=percutaneous coronary intervention; QOL=quality of life; R=randomized; U.S.=United States; wks=weeks; yrs=years