



Department of Vermont Health Access

Therapeutic Class Review Direct Vasodilators Combination Products

Overview/Summary

The fixed-dose combination hydralazine/isosorbide dinitrate is indicated as an adjunct to standard therapy for heart failure in self-identified African American patients. Direct vasodilators have limited effectiveness as single entity agents and are not usually used as monotherapy. The addition of a direct vasodilator to other agents for the treatment of heart failure should be considered mainly in patients who have not responded adequately to recommended first-line drug regimens.¹⁻⁴

All direct vasodilators function through a direct vasodilatory effect on vascular smooth muscle.^{5,6} This vasodilation results in decreased arterial blood pressure (diastolic more than systolic), decreased peripheral vascular resistance, and a compensatory increase in heart rate, stroke volume, and cardiac output. Another compensatory response is decreased renal sodium excretion and increased plasma volume; consequently, a diuretic such as hydrochlorothiazide is often used to offset this effect.^{6,7}

The organic nitrates induce relaxation of vascular smooth muscle, resulting in dilation of peripheral arteries and veins.⁸⁻¹⁰ Venous dilation reduces left ventricular end-diastolic pressure and pulmonary capillary wedge pressure (preload). The dilation of the arteries causes a reduction in systemic vascular resistance, systolic arterial pressure and mean arterial pressure (afterload).^{11,12} The vasodilatory effects of nitrates are least pronounced in the arterioles, and this selective vasodilation can have useful effects, as when nitrates are used to treat angina.^{8,9} In the treatment of heart failure, hydralazine and nitrates are used in combination because hydralazine selectively dilates arterioles and nitrates dilate veins which is important in patients that do not respond to other therapy.¹⁰ Frequent repeated or continuous exposure to organic nitrates leads to a decrease in their pharmacological effects. Tolerance to nitrates is a result of dose and frequency of administration of the preparation. The development of tolerance limits the efficacy of all chronic nitrate therapies regardless of route. Nitrate-free interval dosing can limit the degree of tolerance produced from chronic nitrate therapy.⁹

The combination product containing hydralazine and isosorbide dinitrate (BiDil[®]) is currently not available generically. Additionally, in January 2008, NitroMed Inc, the manufacturer of BiDil[®], announced that it was discontinuing sales and promotional activities for BiDil[®] although it will continue to make it available for patients. NitroMed also reported its intentions to proceed with development of a longer-acting, once-daily version of BiDil[®].¹³

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade Name)	Medication Class	Generic Availability
Hydralazine/isosorbide dinitrate (BiDil [®])	Combination direct vasodilators	-

Indications

Table 2. Food and Drug Administration (FDA) Approved Indications¹¹

Indication	Hydralazine/Isosorbide Dinitrate
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	✓

Indication	Hydralazine/Isosorbide Dinitrate
functional status	

Pharmacokinetics

Table 3. Pharmacokinetics¹¹

Generic Name	Bioavailability (%)	Metabolism	Active Metabolites	Elimination	Half-Life (hours)
Hydralazine	10 to 26	Liver: acetylation, hydroxylation, conjugations with pyruvic acid	None to minimal activity	Renal	4
Isosorbide dinitrate	10 to 90	Extensive First-pass metabolism in liver	Yes, 2-mononitrate and 5-mononitrate	Renal	2

Clinical Trials

Concurrent administration of hydralazine and isosorbide dinitrate has proven to be beneficial in the treatment of heart failure.¹⁴⁻¹⁹ Clinical benefit was shown in studies in which hydralazine and isosorbide dinitrate were administered concomitantly as individual components and as a fixed-dose combination product.¹⁵⁻¹⁹ The V-HeFT I study reported a 34% risk reduction in mortality by two years in men with impaired cardiac function and reduced exercise tolerance who received concurrent treatment with hydralazine and isosorbide dinitrate.¹⁸ The A-HeFT trial reported lower mortality rates with the fixed-dose combination product compared to placebo in African American patients with moderate-to-severe symptomatic heart failure.¹⁵⁻¹⁷

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Unverferth et al¹⁴</p> <p>Hydralazine 225 mg/day in 3 divided doses</p> <p>vs</p> <p>ISDN 160 mg/day in 4 divided doses</p> <p>vs</p> <p>hydralazine 225 mg/day in 3 divided doses plus ISDN 160 mg/day in 4 divided doses</p> <p>vs</p> <p>placebo</p>	<p>DB, PC, RCT</p> <p>Patients with left ventricular end-diastolic pressure > 10 mm Hg, angiographic ejection fraction < 50%, no narrowing >50% in diameter in any coronary artery</p>	<p>N=49</p> <p>3 months</p>	<p>Primary:</p> <p>Change from baseline at three months in echocardiographic percent change of left ventricular diameter (% Δ D), the systolic time intervals ratio of pre-ejection period /left ventricular ejection time, the pulmonary capillary wedge pressure, mean pulmonary artery pressure, pulmonary vascular resistance, cardiac index, and systemic vascular resistance</p> <p>Secondary:</p> <p>Not reported</p>	<p>Primary:</p> <p>For the % Δ D and pre-ejection period/left ventricular ejection time, a significant improvement from baseline with hydralazine monotherapy and combination therapy ($P<0.05$) was seen compared to no significant changes from baselines with ISDN monotherapy or placebo therapy.</p> <p>There was a significant decrease from baseline with ISDN monotherapy and combination therapy in pulmonary capillary wedge pressure, mean pulmonary artery pressure, and the pulmonary vascular resistance ($P<0.05$) compared to no significant changes from baseline with hydralazine monotherapy and placebo therapy.</p> <p>Hydralazine monotherapy resulted in a decrease in systemic vascular resistance ($P<0.01$) and increase in cardiac index from 2.5 ± 0.4 to 3.1 ± 0.4 L/min/m² ($P<0.05$).</p> <p>Combination therapy resulted in a decrease in SVR and cardiac index increased from 2.3 ± 0.4 to 3.1 ± 0.4 L/min/m² ($P<0.01$).</p> <p>There was no improvement in systemic vascular resistance or cardiac index with ISDN monotherapy or placebo therapy.</p> <p>Myocardial cell diameter decreased from 25.4 ± 3.1 microns at baseline to 23.1 ± 3.8 microns with hydralazine monotherapy ($P<0.05$). Combination therapy decreased its cell diameter from 23.9 ± 3.7 to 22.2 ± 2.2 microns ($P<0.05$).</p> <p>There was no change in the myocardial cell diameter seen in patients treated with ISDN monotherapy or with placebo therapy.</p> <p>Secondary:</p> <p>Not reported</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Taylor et al¹⁵ A-HeFT</p> <p>Hydralazine/ISDN 37.5/20 mg three times daily titrated up to hydralazine/ISDN 75/40 mg three times daily</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, RCT</p> <p>Patients ≥18 years of age, self-identified as of African descent, with NYHA class III or IV heart failure on standard therapy for at least 3 months and evidence of left ventricular dysfunction within the prior 6 months</p>	<p>N=1,050</p> <p>18 months (mean duration of follow-up was 10 months)</p>	<p>Primary: A composite score made up of weighted values for death from any cause, a first hospitalization for heart failure, and quality of life changes</p> <p>Secondary: Individual components of the primary composite score</p>	<p>Primary: From a range of possible scores of –6 to 2 for the composite endpoint, patients in the active treatment group achieved a significantly better score of –0.1±1.9 compared to –0.5±2.0 in the placebo group (<i>P</i>=0.01).</p> <p>Secondary: There was a significantly higher mortality rate in the placebo group compared to the hydralazine/ISDN group (6.2 vs 10.2%; <i>P</i>=0.02). Survival was increased by 43% in the active treatment group (HR, 0.57; <i>P</i>=0.02). This led to the early termination of the trial.</p> <p>Compared to the placebo group, the rate of first hospitalization for heart failure was significantly reduced in the hydralazine/ISDN group (16.4 vs 24.4%; <i>P</i>=0.001).</p> <p>There was a significant improvement in quality of life scores found with the hydralazine/SDN group when compared to the placebo group (–5.6±20.6 vs –2.7±21.2; <i>P</i>=0.02).</p>
<p>Taylor et al¹⁶ A-HeFT</p> <p>Hydralazine/ISDN 37.5/20 mg three times daily titrated up to hydralazine/ISDN 75/40 mg three times daily</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, RCT</p> <p>Post-hoc analysis of A-HeFT</p>	<p>N=1,050</p> <p>Mean duration of follow-up was 18 months</p>	<p>Primary: Cause specific mortality, event free survival (time to either death or first hospitalization and time to first hospitalization for heart failure</p> <p>Secondary: Subgroup analysis</p>	<p>Primary: Cardiovascular deaths were significantly reduced in the treatment group compared to the placebo group (5.0 vs 8.5%; <i>P</i>=0.027). Pump failure death was also significantly reduced (75%) compared to the placebo group (0.8 vs 3.0%; <i>P</i>=0.012). There were no significant differences between the groups for other causes of death.</p> <p>In the treatment group event-free survival (death or first hospitalization for heart failure) was significantly improved compared to the placebo group (HR, 0.63; 95% CI, 0.49 to 0.81; <i>P</i><0.001).</p> <p>The time to first hospitalization for heart failure was also significantly reduced (HR, 0.61; 95% CI, 0.46 to 0.80; <i>P</i><0.001).</p> <p>Secondary: A consistent beneficial effect was seen in the treatment sub groups (age, sex, baseline blood pressure, history of chronic renal</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Yancy et al¹⁷ X-A-HeFT</p> <p>Hydralazine/ISDN 37.5/20 mg three times daily titrated up to hydralazine/ISDN 75/40 mg three times daily</p> <p>vs</p> <p>placebo</p>	<p>ES, OL</p> <p>Patients previously enrolled in A-HeFT with NYHA class I to IV heart failure symptoms while receiving background therapy and satisfying the A-HeFT inclusion criteria</p>	<p>N=158</p> <p>12 months or until hydralazine/ISDN approved by the FDA</p>	<p>Primary: Compliance with study drug, safety, tolerability</p> <p>Secondary: Change in NYHA association class, death, hospitalization for heart failure</p>	<p>insufficiency, presence of diabetes, cause of heart failure, and baseline medication use) on primary composite score and event-free survival.</p> <p>Primary: Compliance in the treatment group averaged 87+25%, with no significant difference when compared to the placebo group.</p> <p>There were no significant differences in adverse events between the groups.</p> <p>Secondary: No significant difference was seen in hospitalizations from heart failure according to randomization.</p> <p>The greatest improvement in heart failure symptoms occurred in NYHA class III (at baseline) compared to other classes ($P<0.001$).</p> <p>Overall most patients were unchanged with 24% showing improved NYHA class and 9% showing a worsening.</p>
<p>Cohn et al¹⁸ V-HeFT I</p> <p>Hydralazine 300 mg daily plus ISDN 160 mg daily</p> <p>vs</p> <p>prazosin 20 mg daily</p> <p>vs</p> <p>placebo</p>	<p>AC, DB, PC, RCT</p> <p>Men with impaired cardiac function and reduced exercise tolerance on digoxin and a diuretic</p>	<p>N=642</p> <p>3 years</p>	<p>Primary: Mortality</p> <p>Secondary: Effect on left ventricular function</p>	<p>Primary: There was a 34% risk reduction in mortality by two years in the hydralazine plus ISDN group compared to the placebo group ($P<0.028$).</p> <p>Cumulative mortality rates of 25.6 and 36.2% were observed in the hydralazine plus ISDN group at two and three years respectively, compared to 34.3 and 46.9% in the placebo group (P value not reported). The results found in the prazosin group were similar to the placebo group.</p> <p>Secondary: A significant increase in the LVEF was reported at eight weeks and one year in the hydralazine plus ISDN treatment group, but not in either the prazosin or placebo groups.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Cohn et al¹⁹ V-HeFT II</p> <p>Hydralazine 75 mg plus ISDN 40 mg four times daily</p> <p>vs</p> <p>enalapril 10 mg twice daily</p>	<p>DB, RCT</p> <p>Men between 18 and 75 years of age receiving digoxin and diuretic therapy for heart failure</p>	<p>N=804</p> <p>2 years</p>	<p>Primary: Mortality, body oxygen consumption at peak exercise, LVEF</p> <p>Secondary: Not reported</p>	<p>Primary: Mortality after two years was significantly lower in the enalapril arm (18%) than in the hydralazine plus ISDN arm (25%; $P=0.016$).</p> <p>Body oxygen consumption at peak exercise was increased only by hydralazine plus ISDN treatment and was significantly greater at 13 weeks, six months and two years ($P=0.01$, $P=0.02$ and $P=0.02$, respectively).</p> <p>LVEF, which increased with both regimens during the two years after randomization, increased more ($P=0.026$) during the first 13 weeks in the hydralazine plus ISDN arm.</p> <p>Secondary: Not reported</p>

Study abbreviations: AC=active-controlled, DB=double-blind, ES=extension study, MC=multicenter, OL=open label, PC=placebo-controlled, RCT=randomized control trial
 Miscellaneous abbreviations: CI=confidence interval, FDA=Food and Drug Administration, HR=hazard ratio, ISDN=isosorbide dinitrate, LVEF=left ventricular ejection fraction, NYHA=New York Heart Association

Special Populations**Table 5. Special Populations¹¹**

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Hydralazine/ isosorbide dinitrate	Safety and efficacy in elderly patients have not been established. Safety and efficacy in children have not been established.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	C	Unknown

Adverse Drug Events**Table 6. Adverse Drug Events (%)¹¹**

Adverse Event	Hydralazine/Isosorbide Dinitrate
Cardiovascular System	
Chest pain	16
Hypotension	8
Palpitations	4
Tachycardia	2 to 4
Central Nervous System	
Asthenia	14
Dizziness	32
Headache	50
Malaise	1 to 2
Somnolence	1 to 2
Dermatologic	
Alopecia	1 to 2
Angioedema	1 to 2
Paresthesia	4
Sweating	1 to 2
Endocrine/Metabolic	
Hypercholesterolemia	1 to 2
Hyperglycemia	4
Hyperlipidemia	3
Gastrointestinal	
Bowel incontinence	✓
Cholecystitis	1 to 2
Nausea	10
Vomiting	4
Respiratory	
Amblyopia	3
Arthralgia	1 to 2
Bronchitis	8
Myalgia	1 to 2
Rhinitis	4
Sinusitis	8
Tendon disorder	1 to 2
Other	
Allergic reaction	1 to 2
Blurred vision	✓

✓ Percent not specified.

Contraindications/Precautions¹¹

Hydralazine/isosorbide dinitrate is contraindicated in patients allergic to any of its components. The warnings and precautions for hydralazine/isosorbide are the same as those for the individual components.

Hydralazine may cause systemic lupus erythematosus-like symptoms and discontinuation of hydralazine/isosorbide dinitrate should be considered if symptoms occur. Hydralazine can cause tachycardia that may potentially lead to myocardial ischemia and anginal attacks. Hydralazine is associated with neuritis including symptoms of paresthesia, numbness and tingling. If these symptoms develop, pyridoxine should be added to hydralazine/isosorbide dinitrate.

Isosorbide dinitrate may aggravate angina caused by hypertrophic cardiomyopathy. Patients with acute myocardial infarction must be monitored to avoid potential hypotension and tachycardia when hydralazine/isosorbide dinitrate is administered. Even small doses of hydralazine/isosorbide dinitrate can cause severe hypotension, particularly in the upright position; therefore, it should not be used in patients that are volume depleted or already hypotensive.

Drug Interactions**Table 7. Drug Interactions^{11,12}**

Drugs	Interaction	Mechanism
Hydralazine	β -adrenergic blocking agents (β -blockers) (metoprolol, propranolol)	Serum levels and hence, pharmacologic effects of both drugs may be enhanced. Hydralazine increases systemic availability of some β -blockers, probably by transient increase in splanchnic blood flow and decreasing first-pass hepatic metabolism
Nitrates and nitrites	Dihydroergotamine	The metabolism of dihydroergotamine is decreased thus increasing its bioavailability. The dose of the dihydroergotamine may need to be decreased.
Nitrates and nitrites	Sildenafil, tadalafil, vardenafil	Sildenafil may potentiate the hypotensive effects of nitrates. The use of these agents in combination is contraindicated.

Dosage and Administration

Combination fixed-dose hydralazine and isosorbide dinitrate is not interchangeable with the associated individual components. However, the individual components are available generically in several dosage strengths, which allows for appropriate titration.

Table 8. Dosing and Administration¹¹

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Hydralazine/ isosorbide dinitrate	<u>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:</u> Initial: 1 tablet (37.5/20 mg) TID; maximum, 2 tablets TID	Safety and efficacy in children have not been established.	Tablet: 37.5/20 mg

TID=three times daily

Clinical Guidelines

Current guidelines are summarized in Table 9. Due to the complexity of treatment regimens for heart failure, the associated guideline summaries focus on the role of hydralazine/isosorbide dinitrate in disease management.

Table 8. Clinical Guidelines

Clinical Guideline	Recommendation
<p>American College of Cardiology/American Heart Association: Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult (2005)¹ and Diagnosis and Management of Heart Failure in Adults (2009 Focused Update)²</p>	<ul style="list-style-type: none"> • The addition of a combination of hydralazine and a nitrate is reasonable for patients with heart failure who are already taking an angiotensin converting enzyme (ACE) inhibitor and β-blocker for symptomatic heart failure, but who have persistent symptoms. • A combination of hydralazine and a nitrate might be reasonable in patients with current or prior symptoms of heart failure and reduced left ventricular ejection fraction (LVEF) who cannot be given an ACE inhibitor or an angiotensin II receptor blocker (ARB) because of drug intolerance, hypotension, or renal insufficiency. • The combination of hydralazine and nitrates is recommended to improve outcomes for patients self-described as African American, with moderate to severe symptoms on optimal therapy with ACE inhibitors, β-blockers and diuretics. • Combination of fixed-dose of hydralazine and isosorbide dinitrate to a standard regimen for heart failure, including ACE inhibitors and β-blockers, is recommended in order to improve outcomes for patients self-described as African American, with New York Heart Association (NYHA) functional class III or IV heart failure. Any potential benefit in other patients has yet to be evaluated. • Patients with heart failure should be given nitrates and β-blockers for the treatment of angina.
<p>Heart Failure Society of America: Heart Failure Society of America 2010 Comprehensive Heart Failure Practice Guidelines (Executive Summary) (2010)³</p>	<ul style="list-style-type: none"> • Combination of hydralazine and isosorbide dinitrate is recommended as part of standard therapy in addition to β-blockers and ACE inhibitors for African Americans with heart failure and reduced LVEF. • In patients with reduced LVEF, combination hydralazine and an oral nitrate may be considered when ACE inhibitors are not tolerated due to hyperkalemia or renal insufficiency or ARBs are not tolerated due to cough or angioedema. • May be considered in non–African American patients with left ventricular dysfunction who remain symptomatic despite optimized standard therapy. • Addition of the combination of hydralazine and isosorbide dinitrate should be considered in African American patients with heart failure and reduced LVEF who have persistent symptoms or progressive worsening despite optimized therapy with ACE inhibitors and β-blocker or unable to tolerate a β-blocker.
<p>European Society of Cardiology: European Society of Cardiology Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure (2008)⁴</p>	<ul style="list-style-type: none"> • Isosorbide dinitrate in combination with hydralazine may be considered for the management of heart failure in cases of intolerance to ACE inhibitors and ARBs. Addition of the combination isosorbide dinitrate and hydralazine should be considered in patients with persistent symptoms despite treatment with an ACE inhibitor, β-blocker and an ARB or aldosterone antagonist.

Conclusions

Hydralazine/isosorbide dinitrate is Food and Drug Administration-approved as an adjunct to standard therapy for the treatment of heart failure in self-identified black patients.¹¹ Clinical trials have demonstrated a reduction in mortality in this population; however, there is limited literature in other populations.¹⁵⁻¹⁷ Due to this, guidelines make specific recommendations for using the combination of hydralazine and isosorbide dinitrate in African American patients after the failure of angiotensin converting enzyme inhibitors and β -blockers.¹⁻⁴ Both hydralazine and isosorbide dinitrate are available

generically; however, generic hydralazine is not available in a strength equivalent to the fixed-dose combination product, which contains 37.5 mg of hydralazine.

Appendix I: Utilization Within This Drug Class for DVHA: January 1, 2011 to June 30, 2011

There was no utilization for direct vasodilators-combination products within this time period.

Recommendations

No changes to the Department of Vermont Health Access (DVHA) approval criteria (see below) for direct vasodilators-combination products are proposed.

Bidil[®]:

- The prescriber provides a clinically valid reason why the patient cannot use isosorbide dinitrate and hydralazine as separate agents.

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