Isosorbide dinitrate is a white to off-white, crystalline powder with the empirical formula C8H8N4·HCl and a molecular weight of 196.64. It is soluble in water, hydralazine hydrochloride is described chemically as 1-hydrazinophthalazine with effects on both arteries and veins, and hydralazine hydrochloride, a predominantly arterial vasodilator.

Metabolism and Elimination: The mechanism of action underlying the beneficial effects of BiDil in the treatment of heart failure has not been established. Isosorbide dinitrate is a vasodilator affecting both arteries and veins. Its dilator effect in patients with heart failure, mean absolute bioavailability of a single oral dose of hydralazine 50 mg and propranolol 1 mg, the Cmax and AUC of isosorbide dinitrate increased by about 143% and 77%, respectively. In healthy subjects administered a single oral dose of hydralazine 50 mg and metoprolol 100 mg, the Cmax and AUC for metoprolol increased by about 50% and 30%, respectively. In propranolol women, multiple doses of hydralazine 25 mg and metoprolol 50 mg bid increased the Cmax and AUC for hydralazine and propranolol, respectively. In healthy men administered single oral doses of hydralazine 25 mg and either isosorbide 20 mg or enalapril 20 mg, 1 μg/kg, the Cmax and AUC for isosorbide 20 mg and enalapril were each about 30%, but statistically significant differences were not observed. Intravenous co-administration of 0.2 mg hydralazine HCl and 40 mg isosorbide dinitrate in patients with congestive heart failure resulted in a 21% increase in cardiac output and the clearance of isosorbide dinitrate.

Isosorbide Dinitrate
A single dose of 20 mg of isosorbide dinitrate was administered to healthy subjects after a 4-hour fast. The Cmax for isosorbide dinitrate was inferior to both nitrates and their metabolites to be observed. The vasodilating effects of coadministered isosorbide dinitrate may be additive to those of other vasodilators, especially alcohol when administered concurrently with isosorbide dinitrate.

BiDil®
No pharmacodynamic drug-drug interaction studies were conducted with BiDil.

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

Clinical Trials
BIDII or a combination of isosorbide dinitrate and hydralazine hydrochloride was provided to two placebo groups, 1,690 patients with mild to severe heart failure (mostly NYHA class II and III) and one active control trial (vs. enalapril) in 804 patients. In the earlier trial V-HeFT II, combination of hydralazine and isosorbide dinitrate 75 mg/40 mg qd (n=186) was compared to placebo (n=273) in men with impaired cardiac function and reduced exercise capacity, output, renal blood flow and limb blood flow, with the combination, however, was not greater than with hydralazine alone. There is no study of hemodynamic effects of multiple dosing.

In a second study of mortality, V-HeFT II, the combination of hydralazine and isosorbide dinitrate 75 mg/40 mg qd was compared to enalapril 40 mg bid in patients with impaired cardiac function and reduced exercise capacity (NYHA class II and III), and on therapy with diuretics, angiotensin-converting enzyme (ACE) inhibitors (75% of patients) and beta-blockers (48%). NYHA III and IV, on therapy with diuretics and diuretics and diuretics. The combination of hydralazine and isosorbide dinitrate was not statistically different from enalapril overall, but retrospective analysis showed that the difference was observed in the white population (p=0.047); there was essentially no difference in the black population (p=0.091). Based on these retrospective analyses suggesting an effect on survival in black patients, but showing little evidence of an effect in the white population, a third study was conducted in patients with and without heart failure.

The A-Heft II trial evaluated BiDil vs. placebo among 1,050 self-identified black patients (95% NYHA class III and 19% NYHA class IV) at 169 centers in the United States. All patients were required to be capable of engaging in moderate exercise, have a LVEF ≤ 50% or left ventricular internal diastolic dimension ≥ 2.9 cm/m² plus NT-pro BNP ≤ 45. Patients were maintained on stable background therapy and randomized to BiDil (n=518) or placebo (n=532). BiDil was initiated at 20 mg isosorbide dinitrate/3.75 mg hydralazine hydrochloride three times daily and titrated to a target dose of 40/75 mg three times daily or to the maximum tolerated dose. Patients were treated for up to 16 months.

Effects on survival and hospitalization for heart failure were similar in subgroup analyses by age, gender, and disease, and use of concomitant medications, as shown in Figure 4.
The effects of BiDil on vasodilators including alcohol may be additive.

Physician carefully weigh the benefits and risks of continued therapy with BiDil.

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

- Headache
- Nervousness
- Angina
- Myocardial infarction
- Cardiac arrest
- Peripheral ulceration
- Paralytic ileus
- Ischemic bowel
- Stroke
- Seizures
- Respiratory distress
- Cardiac tamponade
- Shock

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

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

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

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

Methemoglobin levels are measurable by most clinical laboratories.