

Company Profile

a report by

NitroMed, Inc.

NitroMed, Inc. (Lexington, MA), is an emerging research-based pharmaceutical company and the manufacturer of BiDil® (isosorbide dinitrate/hydralazine hydrochloride). BiDil was approved by the US Food and Drug Administration (FDA) in June 2005 and is marketed by NitroMed through a dedicated sales force. The medicine is indicated for the treatment of heart failure (HF) as an adjunct to current standard HF therapy in self-identified black patients to improve survival, prolong time to hospitalization for HF and improve patient-reported functional status. The FDA approval of BiDil was based primarily on the efficacy data from the company's landmark African American Heart Failure Trial (A-HeFT), as well as the unanimous recommendation for approval from the FDA Cardiovascular and Renal Drugs Advisory Committee.

A-HeFT – co-sponsored by NitroMed and the Association of Black Cardiologists, Inc. – was the first study conducted in a HF population in which all of the participants identified themselves as black. This phase 3 trial commenced in June 2001 and evaluated the effects of BiDil in black patients when taken in addition to current standard HF therapies. After a unanimous recommendation from the independent A-HeFT Data and Safety Monitoring Board (DSMB) and Steering Committee in July 2004, A-HeFT was halted early due to a significant survival benefit seen with the drug.

In A-HeFT, most patients received (in addition to BiDil or placebo) a loop diuretic, an angiotensin converting enzyme (ACE) inhibitor or an angiotensin-2 receptor blocker (ARB) and a beta-blocker, and many also received a cardiac glycoside or an aldosterone antagonist. Self-identified black patients taking BiDil in addition to current standard HF therapies experienced a significant 43% decrease in the risk of mortality (($P=0.012$) absolute mortality rate: BiDil 6.2% versus placebo 10.2%), a 39% reduction in the risk of first hospitalization for HF ($P<0.001$) (absolute first hospitalization rate: BiDil 16.4% versus placebo 24.4%) and a statistically significant improvement at most time points in response to the Minnesota Living with Heart Failure® Questionnaire (MLHF-Q), which is a self-report of the patient's

functional status versus patients taking placebo. The results from A-HeFT were presented at the American Heart Association's (AHA's) 2004 Scientific Sessions and were published in the November 2004 issue of the *New England Journal of Medicine*.

The Genetic Risk Assessment in Heart Failure trial (GRAHF) is a study currently underway to help determine which subsets of African Americans had the greatest response to BiDil, based on the identification of specific shared biomarkers. In addition, GRAHF may provide information that could help identify new patient subsets where BiDil may be effective. Information from these studies and other studies of biomarkers may facilitate the future tailoring of the most appropriate drug combinations for HF treatment.

NitroMed is focused on the research, development and commercialization of proprietary pharmaceuticals based on the therapeutic benefits of the naturally occurring molecule nitric oxide (NO). NitroMed plans to build on the BiDil development experience and commercialization infrastructure by identifying and marketing additional pharmaceutical products for cardiovascular disease (CVD). NitroMed is also applying NO technology with the goal of developing new treatments, as well as safer and more effective versions of existing treatments. Research and development (R&D) efforts focus on major diseases that are characterized by a deficiency in NO, such as CVD.

Important Safety Information

- Augmentation of the vasodilatory effects of isosorbide dinitrate by phosphodiesterase inhibitors (e.g. Viagra®/Revatio™, Levitra® and Cialis®) could result in severe hypotension.
- Treatment with hydralazine may produce a clinical picture simulating systemic lupus erythematosus (SLE) including glomerulonephritis. If SLE-like symptoms occur, discontinuation of BiDil should be considered. Residua have been detected many years after the discontinuation of hydralazine.



- Symptomatic hypotension may occur even with small doses of BiDil. It should be used with caution in volume depleted or hypotensive patients.
- Headache (50%) and dizziness (32%) were the two most frequent adverse events and were more than twice as frequent in the BiDil group.* ■
- Hydralazine can cause tachycardia potentially leading to myocardial ischemia and anginal attacks.
- Caution should be exercised if BiDil is used with antidepressants monoamine oxidase (MAO) inhibitors, alcohol, sildenafil, vardenafil or tadalafil.

Contact Information

www.BiDil.com

*Viagra is a registered trademark and Revatio is a trademark of Pfizer, Inc.; Levitra is a registered trademark of Bayer Healthcare, GlaxoSmithKline, and Schering-Plough; Cialis is a registered trademark of Lilly ICOS LLC®.