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## Diovan® the first blood pressure medication in a large-scale clinical trial to lower C-reactive protein, an important marker of inflammation

*High doses of Co-Diovan (valsartan/hydrochlorothiazide) helped significant number of hard-to-treat patients rapidly reach target blood pressure*

**Basel, May 19, 2006** – Diovan® (valsartan) lowered the level of the inflammatory marker high sensitivity C-reactive protein (hsCRP), independently of its established efficacy in lowering blood pressure, according to findings presented today at the American Society of Hypertension, Inc. Annual Scientific Meeting and Exposition (ASH 2006) and published online in *Hypertension* later today.

The study also showed that Diovan and Co-Diovan, including two new high doses recently approved by the US Food and Drug Administration (FDA), helped a significant number of hard-to-treat patients with moderate to severe high blood pressure quickly achieve blood pressure goals in as little as two weeks.<sup>1</sup>

“Increased hsCRP levels are commonly found in those patients at increased risk for cardiovascular events,”<sup>2</sup> said Dr. Paul Ridker, MD, MPH, Eugene Braunwald Professor of Medicine at the Harvard Medical School and Brigham and Women’s Hospital and lead investigator of the Val-MARC trial (Valsartan-Managing blood pressure Aggressively and evaluating Reductions in hsCRP).

“Until now, statins were among only a few medicines known to lower hsCRP. This study showed that treating high blood pressure with valsartan can also reduce levels of this important inflammatory marker,” said Dr. Ridker.

These new findings are from Val-MARC, a large randomized clinical trial conducted in a diverse range of moderate to severe high blood pressure patients. Val-MARC is the largest study to investigate whether a blood pressure medication can also lower hsCRP.

In Val-MARC, the reductions in hsCRP levels observed with Diovan were preserved in all subgroups in the trial, including those patients who were taking statins. There was no consistent effect observed with Co-Diovan on levels of hsCRP. Val-MARC also demonstrated that Co-Diovan, including two new higher strengths recently approved by the FDA, produced double-digit blood pressure reductions. These reductions are consistent with other data at ASH 2006 that formed the basis of the recent FDA approval.<sup>3</sup>

The new strengths of Co-Diovan provide physicians with the widest range of dosing options in the angiotensin receptor blocker class to help them more effectively address what is rapidly becoming a public health crisis. Seven out of 10 people who receive treatment to lower high blood pressure aren’t maintained in the target zone of 120/80 – 140/90 mmHg.<sup>4</sup> Control of elevated blood pressure can prevent potentially life-threatening consequences such as heart

attack, stroke, heart failure or damage to vital organs.<sup>5</sup> In fact, the risk of cardiovascular disease halves with every decrease of 20/10 mmHg above a healthy blood pressure of 115/75 mmHg.<sup>6</sup>

“Val-MARC is the latest achievement from our robust clinical trial program for Diovan, which has helped this powerful blood pressure medicine become the number one drug in its class,” said Ameet Nathwani, Global Head of Cardiovascular and Metabolic Clinical Research & Development at Novartis Pharma AG.

The Diovan clinical trials program involves more than 100,000 patients across the cardiovascular continuum. As part of the extended Phase IV program, the results of Val-MARC will be further explored in the MADE-ITT trial, which will examine the effects of Diovan, Co-Diovan and hydrochlorothiazide alone on insulin sensitivity and a range of inflammatory markers including hsCRP.

Another ongoing trial is NAVIGATOR, the first and largest study designed to understand the progression and prevention of diabetes and cardiovascular disease, assessing the delay or prevention of cardiovascular events and type 2 diabetes in patients with impaired glucose tolerance.

The megatrials VALUE, VALIANT, and Val-HEFT have already demonstrated the unsurpassed blood pressure-lowering efficacy and cardioprotective benefits of Diovan and Co-Diovan.<sup>7-9</sup>

#### Study details

Val-MARC was conducted in 384 primary care clinics across the U.S. in hard-to-treat high blood pressure patients, including multiple ethnic populations, those with diabetes and the elderly. A prospective, randomized, blinded-endpoint, open-label, community-based study, Val-MARC compared the efficacy of Diovan alone (160 mg force-titrated to 320 mg at week two) versus Co-Diovan (160/12.5 mg force-titrated to 320/12.5 mg at week two) as initial therapy for 1,668 patients with moderate to severe hypertension (defined as systolic blood pressure between 160-185 mmHg and/or diastolic blood pressure of 100-109 mmHg). The trial was designed to examine the effect of Diovan on hsCRP levels and whether this was independent of blood pressure-lowering efficacy. The primary blood pressure and inflammation endpoints were measured at the six week time point. After six weeks of therapy in either arm, physicians were allowed to prescribe an additional 12.5 mg hydrochlorothiazide if a patient’s blood pressure was still uncontrolled.

The median change in hsCRP from baseline after six weeks in the Diovan monotherapy group was -0.12 mg/L compared with +0.05 mg/L in the Co-Diovan group, representing a difference between the treatment groups of 13.3% ( $p < 0.001$ ). The reduction in hsCRP in patients treated with Diovan monotherapy was observed in all subgroups examined in the trial. No relationship was observed between the change in hsCRP levels and blood pressure reductions, suggesting the hsCRP-lowering effect of Diovan is independent of the agent’s blood pressure efficacy.

Baseline blood pressure levels in Val-MARC were 164/101 mmHg and 165/101 mmHg in the Diovan and Co-Diovan arms respectively. At six weeks, the systolic and diastolic blood pressure of the participants in the Diovan monotherapy group dropped a median of 18 mmHg and 9 mmHg ( $p < 0.0001$  from baseline), respectively. Blood pressure was reduced from baseline by a median of 22 mmHg and 12 mmHg ( $p < 0.0001$ ) at 12 weeks after physicians were allowed to prescribe the 320/12.5 mg Co-Diovan at their discretion. Blood pressure of patients in the Co-Diovan arm was reduced by 25 mmHg and 14 mmHg (systolic and diastolic respectively,  $p < 0.0001$ ) at six weeks, and was further reduced from baseline by a median of 27 mmHg and 14 mmHg ( $p < 0.0001$ ) respectively, when physicians could prescribe 320/25 mg Co-Diovan for an

additional six weeks at their discretion. The blood pressure response was consistent across all patient populations studied.

After the moderate to severe patients in Val-MARC were treated with only two weeks of the initial starting dose of Diovan 160 mg or Co-Diovan 160/12.5 mg, 22% and 37% respectively reached a blood pressure goal of <140/90 mmHg. At six weeks, goal rates increased to 32% and 48% and at 12 weeks further increased to 42% and 52% of patients in the Diovan and Co-Diovan groups, respectively.

#### **About Diovan and Co-Diovan**

Novartis remains in the forefront of cardiovascular medicine through development of innovative products like Diovan, the number one prescribed ARB in the world today. Diovan is available as a powerful first-line treatment for high blood pressure in more than 90 countries, for the treatment of heart attack survivors in 71 countries and in 86 countries for the treatment of people with heart failure. Additional marketing authorization applications are pending for the treatment of post-heart attack and heart failure. For high-risk heart attack patients, Diovan last year completed the EU Mutual Recognition Procedure (MRP) in 14 countries for the treatment of clinically stable patients with symptomatic heart failure or asymptomatic left ventricular systolic dysfunction after a recent myocardial infarction. For heart failure, Diovan also completed an EU type 2 variation application in 14 countries for the treatment of people with symptomatic heart failure when ACE inhibitors cannot be used, or as add-on therapy to ACE inhibitors when beta blockers cannot be used. Two higher doses of Co-Diovan, as used in Val-MARC, have recently been approved by the FDA to help more patients successfully manage high blood pressure.

The foregoing release contains forward-looking statements that can be identified by terminology such as “will be further explored,” “will examine”, or similar expressions, or by express or implied discussions regarding potential new indications or labeling for Diovan or Co-Diovan, or regarding potential future sales of these products. Such forward-looking statements involve known and unknown risks, uncertainties and other factors that may cause actual results with Diovan or Co-Diovan to be materially different from any future results, performance or achievements expressed or implied by such statements. There can be no guarantee that Diovan or Co-Diovan will be approved for any additional indications or labeling in any other market. Nor can there be any guarantee regarding potential future sales of Diovan or Co-Diovan. In particular, management's expectations regarding these products could be affected by, among other things, additional analysis of existing clinical data; new clinical data; unexpected clinical trial results; unexpected regulatory actions or delays or government regulation generally; the company's ability to obtain or maintain patent or other proprietary intellectual property protection; competition in general; industry, government, and general public pricing pressures; and other risks and factors referred to in Novartis AG's current Form 20-F on file with the US Securities and Exchange Commission. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those anticipated, believed, estimated or expected. Novartis is providing the information in this press release as of this date and does not undertake any obligation to update any forward-looking statements contained in this press release as a result of new information, future events, or otherwise.

## About Novartis

Novartis AG (NYSE: NVS) is a world leader in offering medicines to protect health, treat disease and improve well-being. Our goal is to discover, develop and successfully market innovative products to treat patients, ease suffering and enhance the quality of life. Novartis is the only company with leadership positions in both patented and generic pharmaceuticals. We are strengthening our medicine-based portfolio, which is focused on strategic growth platforms in innovation-driven pharmaceuticals, high-quality and low-cost generics, human vaccines and leading self-medication OTC brands. In 2005, the Group's businesses achieved net sales of USD 32.2 billion and net income of USD 6.1 billion. Approximately USD 4.8 billion was invested in R&D. Headquartered in Basel, Switzerland, Novartis Group companies employ approximately 96,000 people and operate in over 140 countries around the world. For more information, please visit <http://www.novartis.com>.

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