

## **Landmark Diovan® (valsartan) mega-trial proves life-saving benefits for heart attack sufferers**

*Diovan is the only cardiovascular agent ever demonstrated by a head-to-head trial to have all the proven benefits of an ACE inhibitor, captopril, in patients following a heart attack.*

*VALIANT further strengthens the profile of Diovan in cardiovascular disease across key standard of care measures like cardiovascular protection, tolerability, blood pressure lowering efficacy and patient persistency with therapy<sup>1</sup>*

Orlando, Florida, 10 November 2003 – The fastest-growing branded high blood pressure treatment in the world, Diovan® (valsartan), is also a potentially life-saving treatment after a heart attack, according to the findings of VALIANT, a major new study announced today at the American Heart Association Scientific Sessions 2003 and published online in the *New England Journal of Medicine*. VALIANT (VALsartan In Acute myocardial iNfarcTion) is the largest long-term study ever conducted in people who have survived a heart attack. This critical new data set helps establish Diovan as a highly desirable and powerful first-line option for an increasingly wide patient population.

“We are very pleased with the results of the VALIANT trial, which showed that Diovan is the first and only angiotensin II receptor blocker (ARB) proven to be as cardioprotective as the current standard of care following a heart attack. When these data are combined with the strong benefits Diovan provides for blood pressure lowering, excellent tolerability and long-term patient persistency with therapy, they are very compelling for patients as well as physicians,” said Joerg Reinhardt, Head of Development, Novartis Pharma AG. Novartis plans to file very soon for a post-MI indication.

Based on VALIANT and the cumulative clinical evidence being gathered for Diovan in hypertension, Novartis will accelerate clinical programs designed to demonstrate that Diovan has important blood pressure lowering, patient compliance and vascular health benefits beyond ACE inhibitors (angiotensin-converting-enzyme inhibitors).

“We believe Diovan is well on its way to becoming the new standard of care and we are committed to its continued success,” added Reinhardt.

### **VALIANT provides important new answers to clinical questions**

A rigorous head-to-head comparison of Diovan against captopril, VALIANT studied 14 703 patients at the highest risk for death following a heart attack (myocardial infarction) for an average of two years. VALIANT also studied the effects of combination treatment with Diovan and the ACE inhibitor in these patients.

VALIANT demonstrated that Diovan has all the established life-saving benefits of captopril in heart attack patients – and was at least as effective as the ACE inhibitor in reducing cardiac events following a heart attack, including repeat heart attacks and hospitalisations for

heart failure. Diovan is the only cardiovascular agent ever demonstrated by a head-to-head trial to have all of the proven benefits of an ACE inhibitor in patients following a heart attack. No added benefits were seen with combination treatment.

“VALIANT was a major international study that will change treatment guidelines,” said Marc Pfeffer, MD, PhD, the chair of the VALIANT study, who is a Professor of Medicine at Harvard Medical School and Senior Physician at Brigham and Women’s Hospital, Boston. “We have proven that valsartan is as effective as an ACE inhibitor at prolonging life and preventing recurrent heart attacks and hospitalisations for heart failure. This is significant because it provides physicians with a new option for treating high-risk heart attack survivors.”

Approved for the first-line treatment of high blood pressure in more than 80 countries and for heart failure in more than 40 countries, Diovan is the most widely prescribed drug in its class – and the fastest growing branded high blood pressure treatment in the world. VALIANT now demonstrates Diovan is an effective option for first-line treatment of high-risk patients following a heart attack.

The co-chair of VALIANT is John McMurray, MD, Professor of Medical Cardiology and Honorary Consultant Cardiologist, Clinical Research Initiative in Heart Failure, University of Glasgow. Data coordination and analysis for VALIANT was conducted at Duke Clinical Research Institute, Durham, North Carolina, under the direction of Robert M. Califf, MD, Director of the Institute and Associate Vice Chancellor for Clinical Research, Duke University Medical Center.

#### **Diovan reduces risk for premature death after heart attack by 25%**

An active-control trial, VALIANT compared Diovan to a proven treatment instead of placebo or sugar pill. VALIANT was designed and statistically powered to prove whether the effects of Diovan on all-cause mortality were comparable to captopril. Its patient population and dosing regimen were intentionally modelled after studies which established the benefits of ACE inhibitors vs. placebo so that a statistical comparison (imputed placebo analysis) could be made of their findings.

“VALIANT demonstrates Diovan preserved 99.6% of the benefits of captopril, meaning it reduced death to the same degree as the proven treatment,” said Professor McMurray. “This finding translates into a 25% reduction in premature death by Diovan in patients at high risk following a heart attack.” Diovan could potentially save 30,000 new lives in the US and 15 000-20 000 new lives in the EU each year.

The findings of VALIANT were consistent across all study endpoints and patient subgroups, regardless of age, gender, race, co-existing medical conditions (e.g. diabetes), or background medications, including beta blockers. While no further benefits were seen in patients who took combination therapy, there was no added mortality and no added cardiovascular morbidity in patients who took a beta blocker with Diovan in combination with the ACE inhibitor.

VALIANT demonstrates that Diovan is well-tolerated in post-heart attack patients. In VALIANT, discontinuations due to adverse events were lowest in the valsartan group and highest in the combination group. Hypotension and renal side effects were limited in number and most common in the group that received both medications together than in either group receiving valsartan or captopril alone. The rate of hypotension and renal dysfunction was slightly higher in the valsartan group than in the captopril group. Reducing the dose of study drug allowed a majority of patients who experienced hypotension or renal dysfunction to continue on study medication, and thus remain on life-saving therapy. Overall, there was a statistically significant higher rate of patient discontinuations due to adverse events in the

captopril group, where more treatment-limiting side effects occurred, including cough, rash and taste disturbance, compared to the valsartan group.

VALIANT was a prospective, multinational, randomised, active-controlled, parallel group trial conducted at 931 centres in 24 countries. Patients were men and women aged 18 and over (not of child-bearing potential) enrolled between 12 hours and 10 days after they suffered a heart attack complicated by temporary (transient) heart failure and/or abnormal pumping of the heart (left ventricular systolic dysfunction). In addition to either Diovan and/or captopril, patients also received recommended background therapy including aspirin, cholesterol-lowering agents (statins) and beta blockers.

Because of its scope and design, ongoing analysis of the VALIANT data will continue to yield valuable new insight for years to come about the care of patients following a heart attack. In addition to the primary findings, five other abstracts based on VALIANT were also presented at the American Heart Association Scientific Sessions 2003 concerning topics ranging from factors contributing to poor outcomes following a heart attack to contemporary post-heart attack treatment patterns.

#### **About heart attack**

Heart attack remains one of the world's deadliest conditions. Every year, 600 000 people from EU countries and 1.1 million Americans suffer a heart attack. High blood pressure is a major risk factor for heart attacks.

While progress has been made in treating heart attacks in the emergency room, people who survive the acute (emergency) phase of a heart attack have permanently damaged hearts and are at greatly increased risk for repeat attacks, heart failure, or other deadly complications. One in three dies within a year after surviving a first heart attack. Half of all heart attacks are repeat attacks.

#### **More than 50 000 patients involved in clinical studies with Diovan**

Diovan is one of the most widely studied cardiovascular agents in the world – and the most widely studied ARB. The Diovan clinical research programme is designed to involve 50 000 patients, including 8000 patients with diabetes, in several major trials investigating potential new applications for Diovan across the cardiovascular continuum from pre-diabetes (impaired glucose tolerance) to heart failure. Val-HeFT (Valsartan Heart Failure Trial), which remains one of the largest studies ever conducted in heart failure, led to the approval of Diovan for use in this disease in more than 40 countries. The next trial to report will be VALUE (Valsartan Antihypertensive Long-Term Use Evaluation), a study of 15 314 hypertensive patients with at least one additional risk factor for cardiovascular events. Another major ongoing study with Diovan is NAVIGATOR (Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research) trial in 9150 pre-diabetes patients at risk for cardiovascular events. Novartis is also conducting VAL-MARC, a study of the effects of Diovan on CRP (c-reactive protein) in 5610 high blood pressure patients. CRP is a strong, independent predictor of cardiovascular risk.

The foregoing release contains forward-looking statements that can be identified by terminology such as “increasingly,” “if successful,” “attempt,” “impute,” “will file,” “expected,” “suggest,” “investigating,” “potential,” “new applications,” or similar expressions, or by discussions regarding potential new indications or labelling for Diovan, or regarding the long-term impact of a patient's use of Diovan. Such forward-looking statements involve known and unknown risks, uncertainties and other factors that may cause actual results with 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 will be approved for any additional indications or labelling in any market. In particular, management's ability to ensure satisfaction of the health authorities' further requirements is not guaranteed and management's expectations regarding commercialisation

of Diovan could be affected by, among other things, additional analysis of Diovan 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; and other risks and factors referred to in the Company's current Form 20-F on file with the US Securities and Exchange Commission. Should one or more of these risks or uncertainties materialise, 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.

Novartis AG (NYSE: NVS) is a world leader in pharmaceuticals and consumer health. In 2002, the Group's businesses achieved sales of CHF 32.4 billion (USD 20.9 billion) and a net income of CHF 7.3 billion (USD 4.7 billion). The Group invested approximately CHF 4.3 billion (USD 2.8 billion) in R&D. Headquartered in Basel, Switzerland, Novartis Group companies employ about 78 200 people and operate in over 140 countries around the world. For further information please consult <http://www.novartis.com>

<sup>1</sup> Wogen, J. et al.: Journal of Managed care Pharmacy 2003; 9:424-9

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Publication of the study results can be viewed online at [www.nejm.org](http://www.nejm.org)

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