New analysis shows Novartis Entresto improves glycemic control in reduced ejection fraction heart failure patients with diabetes

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- New post-hoc analysis of PARADIGM-HF data demonstrates Entresto lowered levels of HbA1c (a measure of glycemic control) by 0.26% vs. 0.16% for ACE-inhibitor enalapril in heart failure with reduced ejection fraction (HFrEF) patients who also had diabetes
- New use of insulin was also reduced by 29% among patients taking Entresto compared to enalapril-treated patients(1)
- Up to 40% of HFrEF patients have diabetes, which is associated with worse cardiovascular outcomes(2)
- New analysis presented today at the American College of Cardiology (ACC) Annual Scientific Session and published in The Lancet Diabetes & Endocrinology

EAST HANOVER, N.J., March 18, 2017 /PRNewswire/ -- Novartis announced today results of a new post-hoc analysis in a subgroup of patients with reduced ejection fraction heart failure (HFrEF) and diabetes suggesting that Entresto® (sacubitril/valsartan) tablets improved glycemic control, as assessed by hemoglobin A1c (HbA1c) testing, compared to ACE-inhibitor enalapril[1]. HFrEF is also known as systolic heart failure (HF)[3]. Entresto is indicated to reduce the risk of cardiovascular (CV) death and hospitalization for HF in patients with chronic HF (NYHA Class II-IV) and reduced ejection fraction[4]. It is not indicated to treat diabetes.

Entresto lowered HbA1c levels – a measure of average blood glucose levels for the past two to three months – after one year of treatment for HF, and this effect was sustained over three years of study follow-up[1]. In the analysis, new use of insulin therapy or oral diabetes agents was also reduced in the Entresto group[1]. The findings are based on data from PARADIGM-HF, the largest clinical trial ever conducted in HF[5], and are simultaneously being presented today at the American College of Cardiology (ACC) 66th Annual Scientific Session & Expo in Washington, D.C. and published in The Lancet Diabetes & Endocrinology.

"Diabetes is a major risk factor in heart failure and is strongly linked to progression of the disease, putting heart failure patients at increased risk of hospitalization and death," said Scott Solomon, MD, Director of Noninvasive Cardiology, Brigham and Women's Hospital, Professor of Medicine, Harvard Medical School, and senior author of the publication. "This analysis suggests that, in addition to the proven heart failure benefits demonstrated in PARADIGM-HF, Entresto may also help tighten glycemic control among heart failure patients with diabetes."

An analysis was conducted of 3,778 HFrEF patients in the PARADIGM-HF trial who were diagnosed with diabetes or had a baseline HbA1c ≥ 6.5% without a reported diagnosis at screening (98% of patients assessed had type 2 diabetes). The investigators compared the effects of Entresto vs. enalapril on glycemic control by measuring patients' HbA1c levels at screening and at one-, two-, and three-year follow-up visits, and by evaluating patients' initiation of oral antihyperglycemic or insulin therapy during the study.

This post-hoc analysis found that Entresto decreased HbA1c levels by 0.26% during the first year of follow-up,

compared to a 0.16% reduction with enalapril (p=0.0023)[1]. Over three years, HbA1c levels remained persistently lower in patients treated with Entresto compared to enalapril, with an overall reduction of 0.14% (95% CI [0.06, 0.23]; p=0.0055)[1]. In addition, 29% fewer Entresto-treated patients initiated insulin therapy to achieve glycemic control (114 (7%) vs. 153 (10%) patients, HR 0.71, 95% CI, 0.56-0.90; p=0.0052)[1]. Entresto was shown to reduce the risk of CV death or HF hospitalization compared with enalapril among patients with or without diabetes at baseline[1,6,7].

"On top of the already well-demonstrated clinical benefits of Entresto, a reduction in HbA1c levels in these type 2 diabetes patients is of great interest and shows us that further research is needed to better understand this metabolic effect of the drug," said Fabrice Chouraqui, President of Novartis Pharmaceuticals Corporation. "Novartis is committed to exploring the full potential of this important medication to maximize its value for heart failure patients managing their chronic condition."

About Heart Failure

Heart failure (HF) is a debilitating and life-threatening condition, which impacts 6.5 million Americans and is the leading cause of hospitalization among Americans over the age of 65[8,9]. About half of people with HF have heart failure with reduced ejection fraction (HFrEF), also known as systolic HF[3,10]. Reduced ejection fraction means the heart does not contract with enough force, so less blood is pumped out[11]. HF presents a major and growing health-economic burden that currently exceeds $30 billion in the United States, which accounts for both direct and indirect costs[12].

Novartis has established the largest global clinical program in the HF disease area across the pharma industry to date. FortiHFy, comprising more than 40 active or planned clinical studies designed to generate an array of additional data on symptom reduction, efficacy, quality of life benefits and real world evidence with Entresto, as well as to extend understanding of heart failure.

About Entresto

Entresto is a twice-a-day medicine that reduces the strain on the failing heart. It does this by enhancing the protective neurohormonal systems (natriuretic peptide system) while simultaneously inhibiting the harmful effects of the overactive renin-angiotensin-aldosterone system (RAAS)[4,13]. Other heart failure medicines only block the harmful effects of the overactive RAAS[3]. Entresto contains the neprilysin inhibitor sacubitril and the angiotensin receptor blocker (ARB) valsartan[4].

Entresto is indicated in the US to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction[4]. Entresto is usually administered in conjunction with other heart failure therapies, in place of an angiotensin converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB)[4]. Entresto film-coated tablets are available in three dosage strengths: 24/26 mg, 49/51 mg, and 97/103 mg (sacubitril/valsartan)[4]. These doses are referred to as 50 mg, 100 mg, and 200 mg in the clinical trial literature including the New England Journal of Medicine publication of the results of PARADIGM-HF. The target maintenance dose of Entresto is 97/103 mg twice daily[4].

Novartis is committed to providing patients with affordable access and resources through Entresto Central. For more information, please call 1-888-ENTRESTO or visit www.entresto.com.

Please visit http://www.pharma.us.novartis.com/product/pi/pdf/entresto.pdf for Entresto full Prescribing Information.

Entresto can harm or cause death to an unborn baby. Patients should talk to their doctor about other ways to treat heart failure if they plan to become pregnant. If a patient gets pregnant while taking Entresto, she should tell her doctor right away.

Patients are not to take Entresto if they are allergic to sacubitril or valsartan or any of the ingredients in Entresto; have had an allergic reaction including swelling of the face, lips, tongue, throat or trouble breathing while taking a type of medicine called angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB); or take an ACE inhibitor medicine. Patients are not to take Entresto for at least 36 hours before or after they take an ACE inhibitor medicine. Patients should talk with their doctor or pharmacist before taking Entresto if they are not sure if they take an ACE inhibitor medicine. Patients are not to take Entresto if they have diabetes and take a medicine that contains aliskiren.

Before they take Entresto, patients should tell their doctor about all of their medical conditions, including if they have kidney or liver problems; are pregnant or plan to become pregnant; are breastfeeding or plan to breastfeed. Patients should either take Entresto or breastfeed. They should not do both.

Patients should tell their doctor about all the medicines they take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. They should especially tell their doctor if they take potassium supplements or a salt substitute; nonsteroidal anti-inflammatory drugs (NSAIDs); lithium; or other medicines for high blood pressure or heart problems such as an ACE inhibitor, ARB, or aliskiren.

Entresto may cause serious side effects including serious allergic reactions causing swelling of the face, lips, tongue, and throat (angioedema) that may cause trouble breathing and death. Patients are to get emergency medical help right away if they have symptoms of angioedema or trouble breathing. Patients are not to take Entresto again if they have had angioedema while taking Entresto. People who are black or who have had angioedema may have a higher risk of having angioedema if they take Entresto. Entresto may cause low blood pressure (hypotension). Patients are to call their doctor if they become dizzy or lightheaded, or they develop extreme fatigue. Entresto may cause kidney problems or an increased amount of potassium in the blood.

The most common side effects were low blood pressure, high potassium, cough, dizziness, and kidney problems.

Please see full Prescribing Information, including Boxed WARNING available at http://www.pharma.us.novartis.com/product/pi/pdf/entresto.pdf.

Patients are encouraged to report negative side effects of prescription drugs to the FDA.
Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Disclaimer
The foregoing release contains forward-looking statements that can be identified by words such as "suggests," "may," "suggesting," "committed," "growing," "of great interest," "potential," "planned," or similar terms, or by express or implied discussions regarding potential new indications or labeling for Entresto, or regarding potential future revenues from Entresto. You should not place undue reliance on these statements. Such forward-looking statements are based on the current beliefs and expectations of management regarding future events, and are subject to significant known and unknown risks and uncertainties. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those set forth in the forward-looking statements. There can be no guarantee that Entresto will be submitted or approved for any additional indications or labeling in any market, or at any particular time. Nor can there be any guarantee that Entresto will be commercially successful in the future. In particular, management's expectations regarding Entresto could be affected by, among other things, the uncertainties

inherent in research and development, including clinical trial results and additional analysis of existing clinical data; regulatory actions or delays or government regulation generally; the company's ability to obtain or maintain proprietary intellectual property protection; general economic and industry conditions; global trends toward health care cost containment, including ongoing pricing pressures; safety, quality or manufacturing issues, and other risks and factors referred to in Novartis AG's current Form 20-F on file with the US Securities and Exchange Commission. 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

Located in East Hanover, NJ Novartis Pharmaceuticals Corporation is an affiliate of Novartis which provides innovative healthcare solutions that address the evolving needs of patients and societies. Headquartered in Basel, Switzerland, Novartis offers a diversified portfolio to best meet these needs: innovative medicines, cost-saving generic and biosimilar pharmaceuticals and eye care. Novartis has leading positions globally in each of these areas. In 2016, the Group achieved net sales of USD 48.5 billion, while R&D throughout the Group amounted to approximately USD 9.0 billion. Novartis Group companies employ approximately 118,000 full-time-equivalent associates. Novartis products are sold in approximately 155 countries around the world. For more information, please visit http://www.novartis.com.

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