# Novartis announces FDA filing acceptance of Entresto® (sacubitril/valsartan) for patients with heart failure with preserved ejection fraction (HFpEF)

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- *Approximately 3 million people in the US suffer from HFpEF, a life-threatening condition associated with frequent heart failure hospitalizations and emergency room visits, for which no treatment currently exists*[1-3]
- *If approved for HFpEF, Entresto would be the first medication with that indication and the only therapy for both types of chronic heart failure: HFpEF and heart failure with reduced ejection fraction (HFrEF)*[3]
- *Filing is based primarily on Phase III data from the PARAGON-HF trial, the largest trial completed in patients with HFpEF and the only study that used an active comparator*[4,5]

**East Hanover, June 24, 2020** — Novartis today announced that the US Food and Drug Administration (FDA) accepted the supplemental New Drug Application (sNDA) for use of Entresto in patients with HFpEF. With no currently approved therapies for HFpEF, if approved by the FDA, Entresto would become the first treatment for the condition and the only medication indicated for both HFpEF and HFrEF, both types of chronic heart failure.[3] It is also the only potential therapy that has been evaluated against an active comparator in a Phase III trial for HFpEF.[5] The FDA is expected to make a decision on the Novartis application for this indication in the first half of 2021.

"This filing acceptance furthers our long-term commitment to fighting cardiovascular diseases and builds on the transformative impact Entresto has had for patients with HFrEF," said Victor Bulto, President, Novartis Pharmaceuticals Corporation. “We are another step closer in our mission to reimagine medicine for patients with HFpEF, who currently face this devastating condition and an endless cycle of re-hospitalizations without effective treatments."

The sNDA is based primarily on Phase III data from the multicenter, randomized, double blind, parallel group, active-controlled PARAGON-HF trial, the largest trial completed in patients with HFpEF, which evaluated long-term efficacy and safety of Entresto vs valsartan in 4822 patients with HFpEF.[4,5] Full results of PARAGON-HF were presented at the European Society of Cardiology (ESC) Congress 2019 and additional analyses were presented at American Heart Association’s (AHA) Scientific Sessions 2019 and American College of Cardiology’s (ACC) Annual Scientific Session Together with World Congress of Cardiology (ACC.20/WCC Virtual).

HFpEF is associated with poor outcomes; patients experience high rates of emergency room visits and hospitalizations for heart failure as well as substantial mortality.[1,2] It currently affects approximately 3 million Americans, encompassing a wide range of patients, including those who often have multiple cardiovascular and metabolic comorbidities.[1,2] HFpEF is a chronic condition where the heart muscle stiffens and loses its ability to relax and fill with enough blood, preventing it from meeting the body’s needs.[6] It is increasing in

prevalence, as are HFpEF-related hospitalizations.[1,7] HFpEF is a complex, multi-system disease for which it is difficult to develop treatments due to its distinct pathophysiology and the varied impact of symptoms among patients, despite decades of research.[7]

Currently, Entresto is an approved treatment for patients with HFrEF, also known as systolic heart failure, which is typically defined as ejection fraction less than 40%.[8,9] This is based on its superiority to the angiotensin-converting enzyme (ACE) inhibitor enalapril, an active comparator, in reducing cardiovascular death and heart failure hospitalizations, as demonstrated in the PARADIGM-HF trial.[10] Entresto is a first-choice therapy that helps improve the heart's ability to pump blood to the body in patients with HFrEF.[8,11] More than 646,000 patients to date have been prescribed Entresto in the US.[12]

**About our longstanding commitment to heart failure**

To reimagine medicine for heart failure patients, Novartis established the largest global clinical program in the HF disease area across the pharma industry to date. Known as FortiHFy, it is comprised of more than 40 clinical studies designed to generate an array of additional data on efficacy, quality of life, patient-reported outcomes and real-world evidence with Entresto, as well as to extend understanding of heart failure. FortiHFy includes trials across HFpEF, such as PARAGON-HF, and Entresto's current indication in HFrEF, such as PARADIGM-HF, PIONEER-HF, TRANSITION and PROVE-HF.

**About Entresto for heart failure with reduced ejection fraction**

Entresto (sacubitril/valsartan) is a prescription medicine used to reduce the risk of cardiovascular death and heart failure hospitalization in people with long-lasting (chronic) heart failure (HFrEF).[8] Entresto is usually used with other heart failure therapies in place of an angiotensin-converting enzyme (ACE) inhibitor or other angiotensin II receptor blocker (ARB) therapy.[8] Entresto is a twice-a-day prescription medicine that works by enhancing the beneficial neurohormonal systems (natriuretic peptide system) while simultaneously inhibiting the harmful effects of the overactive renin-angiotensin-aldosterone system (RAAS).[8,13] Most other heart failure medicines only block the harmful effects of the overactive RAAS. Entresto contains the neprilysin inhibitor sacubitril and the ARB valsartan.[8] Entresto film-coated tablets are available in three dosage strengths: 24/26 mg, 49/51 mg and 97/103 mg (sacubitril/valsartan).[8] 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.[8] In adult patients, the target maintenance dose of Entresto is 97/103 mg twice daily as tolerated by the patient.[8]

**IMPORTANT SAFETY 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 an ACE inhibitor or 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; or a history of hereditary angioedema; 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 in adults 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.

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.

**About Novartis**

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