Novartis announces positive FDA Advisory Committee recommendation for use of Entresto® to treat patients with HFpEF

Dec 15, 2020

- The Committee voted 12 to 1 that the data presented support the use of Entresto in treatment of patients with heart failure with preserved ejection fraction (HFpEF)
- Potential Q1 2021 sNDA approval could make Entresto the first therapy indicated for use in treatment of patients with both major types of chronic heart failure: HFpEF and HFrEF; and the only chronic heart failure treatment studied in both conditions against active comparators(1,2)
- HFpEF patients currently have no approved treatment options and face worsening symptoms that result in frequent HF hospitalizations, emergency room and urgent office visits(1,3,4)

EAST HANOVER, December 15, 2020--Novartis today announced that the US Food and Drug Administration (FDA) Cardiovascular and Renal Drugs Advisory Committee (CRDAC) voted 12 to 1 that the data presented support the use of Entresto® (sacubitril/valsartan) in treatment of patients with heart failure with preserved ejection fraction (HFpEF). This was based on data supporting the benefit of Entresto in reducing worsening heart failure (total heart failure [HF] hospitalizations and urgent HF visits) in patients studied in PARAGON-HF. If approved by the FDA, Entresto could become the first therapy indicated for use in treatment of patients with HFpEF, as well as the first medication approved for both major types of chronic heart failure, HFpEF and heart failure with reduced ejection fraction (HFrEF), both based on trials that included active comparators (valsartan and enalapril, respectively).[1,2]

With no approved therapies for HFpEF to address the prevention of HF hospitalizations and urgent visits, a significant unmet medical need exists for a treatment to reduce the burden associated with this debilitating condition. The FDA is expected to make a decision on the supplemental New Drug Application (sNDA) in the first quarter of 2021.

"Managing HFpEF has historically been a clinical and scientific challenge due to the heterogeneity of the condition," said Scott Solomon, MD, Professor of Medicine at Harvard Medical School and Brigham and Women's Hospital, and PARAGON-HF Executive Committee Co-Chair. "Today's vote represents much needed progress in this area of unmet need and is a positive step toward bringing a potential therapy to millions of patients suffering from this type of heart failure."

The Committee's positive decision is based on the totality of evidence from efficacy and safety analyses, including findings presented from a pre-specified subgroup analysis of PARAGON-HF, the largest and only Phase III active-controlled study to date in patients with HFpEF and additional evidence from PARAMOUNT (a Phase II trial in HFpEF), as well as PARADIGM-HF (a Phase III trial in HFrEF).[5-7] Data from PARAGON-HF demonstrated a favorable safety profile for Entresto in patients with HFpEF, which is in line with the vast clinical and post-marketing experience in HFrEF, and showed clinical benefit of Entresto in HFpEF patients.[2]

"Our commitment to reimagine medicine through our extensive clinical trials program on heart failure has been unwavering, and we are encouraged by the Committee's response today," said David Soergel, MD, Global

Head of Cardiovascular, Renal and Metabolic Drug Development, Novartis. "We appreciate the valuable insights shared by the patient and advocacy community about this devastating disease, and we look forward to FDA's decision on the potential approval of this new indication."

HFpEF affects more than 3 million Americans, and is increasing in prevalence as the population ages.[3,8] It is a complex disease for which it is difficult to develop treatments due to its heterogeneous pathophysiology and the varied impact of symptoms among patients, despite decades of research.[9] HFpEF can change the structure of the heart and occurs when the muscle tissue of the heart thickens and stiffens so that it cannot expand to fill with enough blood to meet the body's needs.[10] HFpEF is associated with high rates of recurring heart failure hospitalizations, emergency room visits and urgent doctor's office appointments.[3,4] Each hospitalization event is associated with worsening long-term prognosis, and approximately one in four patients are re-admitted for heart failure within one year of discharge.[11,12]

Entresto is approved in 115 countries worldwide for the treatment of HFrEF, with more than 2.6 million patient-years of exposure to date.[13]

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, including PARAGON-HF, PARAMOUNT and PARAGLIDE-HF, as well as 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).[14] 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.[14] 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).[14,15] Most other heart failure medicines only block the harmful effects of the overactive RAAS. Entresto contains the neprilysin inhibitor sacubitril and the ARB valsartan.[14] Entresto film-coated tablets are available in three dosage strengths: 24/26 mg, 49/51 mg and 97/103 mg (sacubitril/valsartan).[14] 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.[14] In adult patients, the target maintenance dose of Entresto is 97/103 mg twice daily as tolerated by the patient.[14]

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

Located in East Hanover, NJ Novartis Pharmaceuticals Corporation – an affiliate of Novartis – is reimagining medicine to improve and extend people's lives. As a leading global medicines company, we use innovative science and digital technologies to create transformative treatments in areas of great medical need. In our quest to find new medicines, we consistently rank among the world's top companies investing in research and development. Novartis employs about 15,000 people in the United States. For more information, please visit https://www.novartis.us.

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