Cross-Discipline Team Leader Executive Summary

Date	04 April 3, 2024
From	Fred Senatore MD, PhD, FACC
Priority or Standard	Standard
NDA/BLA # and Supplement#	218591
Applicant	Novartis Pharmaceuticals
Date of Submission	14 June, 2023
PDUFA Goal Date	14 April, 2024
Proprietary Name	Entresto
Established or Proper Name	Sacubitril / Valsartan
Dosage Form(s)	Oral Tablet; Sprinkle (Oral Pellets); Extemporaneous Oral Suspension
Applicant Proposed Indication(s)/Population(s)	• to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure. Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal. • for the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older. ENTRESTO reduces NT-proBNP and is expected to improve cardiovascular outcomes.
Applicant Proposed Dosing Regimen(s)	(b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	As above
Recommended Dosing Regimen(s)	As above

This cross-discipline team leader review is based on the following reviews:

Materials Reviewed		
Reviews		
#	**Discipline (Date)**	**Reviewers**
1	Clinical	Clinical Review Template Entresto-Efficay.docx
2	Clinical Pharmacology	Clin_Pharm_NDA207620_NDA218591_S25.p
3	Office of Product Quality	NDA-218591-ORIG1_IQA_1.pdf

Summary of Regulatory Action

Based on the clinical, clinical pharmacology and product quality reviews, approval of the Entresto sprinkles (i.e., Oral Pellets) formulation is recommended at the proposed weight-based posology.

Background

Entresto is a first-in-class angiotensin receptor-neprilysin inhibitor (ARNI), a combination drug product containing an angiotensin receptor blocker (ARB), valsartan, and a neprilysin inhibitor, sacubitril. Entresto was initially approved in 2015 (NDA-207620) based on results from the phase 3 trial PARADIGM-HF, leading to the indication to reduce the *of* risk of cardiovascular death and hospitalization for heart failure (HF) in adults with chronic HF and reduced ejection fraction (HFrEF).

In 2021, Entresto was approved for the same indication with an expanded range of left ventricular ejection fraction (LVEF), based on the PARAGON-HF trial. The revised indication was *"to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure. Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal."*

In 2019, Entresto was approved for a pediatric indication to treat "*symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older. ENTRESTO reduces NT-proBNP and is expected to improve cardiovascular outcomes.*" The basis of the pediatric approval was the PANORAMA-HF trial (NDA-207620/S-013), a 52-week study with a planned sample size of 360 pediatric subjects with HF, evaluating superiority of Entresto over enalapril. The PANORAMA-HF trial was designed under a written request (WR). The primary efficacy endpoint was a global rank of events evaluated through 52 weeks, derived by ranking patients (worst-to-best outcome) based on Category 1 events (i.e., death, listing for

heart transplant, ventricular assist device, extra-corporeal membrane oxygenation, intra-aortic balloon pump) and Category 2 events (i.e., worsening of heart failure). Secondary efficacy endpoints included time to first occurrence of category 1 and 2 events, change in NYHA /Ross functional class through 52 weeks, and change in patient global impression of severity score from baseline through 52 weeks.

Because of enrollment difficulties, the WR was amended to permit an interim analysis at 12 weeks to assess the treatment effect on the bridging biomarker, N-terminal pro-brain natriuretic peptide (NT-proBNP) in fulfillment of the WR requirement. The bridging biomarker strategy relied on the PARADIGM-HF trial in adults with dilated cardiomyopathy that demonstrated an association between reduction in clinical events and reduction of NT-proBNP. A comparable 50% reduction in NT-proBNP observed in the PANORAMA-HF trial (i.e., the bridge) at the 12-week interim analysis inferred a treatment benefit for clinical events, thus yielding an approval of ENTRESTO in the pediatric population.

The applicant now submitted NDA-207620/S-025 detailing the bridging biomarker data in 110 subjects from PANORAMA-HF at week 52. The PANORAMA-HF trial failed to show superiority of Entresto to enalapril for the clinical primary or secondary efficacy endpoints. However, the 52-week data showed a 65% reduction in NT-proBNP from baseline, suggesting a persistence of effect on the biomarker.

As part of the WR, the applicant was required to develop and evaluate an appropriate pediatric dosage form (granules, oral pellets). Concomitant to NDA-207620/S-025, the applicant submitted NDA-218591, the subject of this review, to register the age-appropriate sprinkle formulation. As described in the NDA-207620/S-025 clinical review, the NDA 218591 submission for the new Entresto Sprinkle (oral pellet) dosage form triggered the Pediatric Research Equity Act (PREA). On February 20th, 2024, the Division of Cardiology and Nephrology (DCN) met with the Pediatric Review Committee (PeRC) to discuss NDA 218591 PREA considerations. As a result of that meeting, a partial waiver was granted for studying pediatric patients <1 month of age because of impracticality consequent to low prevalence of HF / Dilated Cardiomyopathy (DCM) in that age group. Furthermore, the results of PANORAMA-HF were deemed to be an adequate assessment of the new dosage form in pediatric patients and that no new studies or assessments were required to fulfill PREA.

This memo focuses on findings from the Office of Product Quality and the Office of Clinical Pharmacology regarding age-appropriate formulations.

Summary Review

Office of Product Quality (OPQ)

OPQ assessed all information on drug substance to be adequate. Drug product information was acceptable and that a shelf life of 36 months (extrapolated from 24 months real-time stability data) was deemed grantable for the drug product stored at 20°C to 25°C.

The manufacturing process was found to be adequate. A pre-approval inspection of the drug product manufacturing facility yielded a recommendation for approval. Other facilities were approved based on previous inspection history.

Biopharmaceutics review concluded that the formulation bridging and dissolution test method information were adequate to support approval. Based on a final conclusion of 'medium' risk with respect to dissolution, correct administration of the dosage form by sprinkling is a requirement of the formulation (swallowing capsules whole is not supported).

Quality labeling concluded that the labeling was adequate following agreement by the applicant to change the dosing form from "granules" to "oral pellets". The reason for this change is "granules" connote shape irregularity, whereas the minitablets in the sprinkle formulation are regular in shape.

Office of Clinical Pharmacology

The Office of Clinical Pharmacology reviewed the results from the completed part 2 of PANORAMA-HF and supported their prior conclusion that it is reasonable to translate the clinical benefit on HF outcomes for ENTRESTO from adults to pediatric patients 1 year to <18 years of age. This conclusion was based on a similar percent change in NT-proBNP from baseline to Week 52 observed between pediatric patients with left ventricular systolic dysfunction and adult DCM HF patients. Additionally, the new oral formulation of Entresto as film-coated granules (oral pellets) with 2 dosage strengths, 6 mg/6 mg (4 film-coated oral pellets) and 15 mg/16 mg (10 film-coated oral pellets) was acceptable. The clinical pharmacology section of the proposed label was updated to include administration instruction for the new granule formulation.

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