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APPLICATION NUMBER:

218591Orig1s000, 207620Orig1s025

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 218591
Supporting document/s:	001
CDER Receipt date:	06/14/2023
Product:	Entresto® (Sacubitril/Valsartan [6 mg/6 mg (4 film-coated granules); 15 mg/16 mg (10 film-coated granules)]
Indication:	Symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older.
Applicant:	Novartis Pharmaceuticals Corporation
Clinical Review Division:	Division of Cardiology and Nephrology (DCN)
Pharm/Tox Division	Division of Pharm/Tox for Cardiology, Hematology, Endocrinology, and Nephrology (DPT-CHEN)
Reviewer:	Narendranath Reddy Chintagari, BVSc & AH (DVM); MVSc, PhD
Supervisor/Team Leader:	Jean Wu, MD, PhD
Pharm/Tox Division Director:	Todd Bourcier, PhD
Project Manager:	Maryam Changi, PharmD

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 218591 are owned by Novartis Pharmaceuticals Corporation (Novartis) or are data for which Novartis has obtained a written right of reference.

Any information or data necessary for approval of NDA 218591 that Novartis does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 218591.

Memorandum:

Novartis Pharmaceuticals Corporation submitted NDA 218591 for marketing of Entresto®, a fixed-dose-combination (FDC) drug (Sacubitril/Valsartan [6 mg/6 mg (4 film-coated granules); 15 mg/16 mg (10 film-coated granules)] via 505(b)(1) pathway. Entresto® in the film-coated tablet formulation has been approved and marketed under NDA207620.

Novartis is also the applicant for the approved NDA 207620 that was initially indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure. Entresto® was later approved (Suppl-13) for the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older based on the interim 12-week data from clinical study#B2319. In this study, the sponsor demonstrated that sacubitril/valsartan reduced in NT-proBNP and therefore expected to improve cardiovascular outcomes. According to Novartis, the safety and tolerability of sacubitril/valsartan in pediatric patients was similar to the adults. The revised label included instructions to prepare extemporaneous suspension using the tablets.

According to Novartis, clinical study#B2319 is now completed and the results were consistent with the interim results. These results have been submitted under NDA 207620 (Suppl-25). Current NDA218591 has been submitted for approval of pediatric formulation. No nonclinical information had been submitted. Nonclinical studies (Module 4) had been cross-referenced to NDA 207620, NDA 020665 [Diovan® (Valsartan, capsule); Applicant: Novartis] and NDA 021283 (Diovan® (Valsartan, tablets); Applicant: Novartis].

The maximum daily dose of Entresto in adults is 97 mg/103 mg. The MDD in pediatric patients depends on the body weight as follows i) body weight below 40 kg: 3.1 mg/kg ii) body weight at least 40 kg and less than 50 kg: 72 mg/78 mg and iii) body weight at least 50 kg: 97 mg/103 mg.

The indication (b) (4) of the proposed new formulation is same as the tablet formulation of Entresto®. The nonclinical sections in the proposed label are same to the respective sections of Entresto® and Diovan® labels. No new impurities of concern have been identified that require safety qualification. No novel excipients are used in the proposed pediatric formulation and the maximum daily intake of individual excipients is less than the respective level listed in FDA-Inactive Ingredient database. Further, the proposed film-coated granules were tested in the pediatric clinical trial. The applicant is referencing NDA 207620 for pediatric clinical trial information. Overall, there is no approvable issue from the Pharmacology/Toxicology perspective.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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