CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218591Orig1s000, 207620Orig1s025

OTHER REVIEW(S)

DIVISION OF CARDIOLOGY AND NEPHROLOGY

RPM Labeling Review

NDAs:	207620-S025/ NDA 218591
Date of submission:	June 14, 2023
Review date:	April 11. 2024
Applicant:	Novartis Pharmaceuticals Corporation
Product:	Entresto (sacubitril/ valsartan)
Reviewers:	Maryam Changi, PharmD Michael Monteleone. MS, RAC
Action date:	April 12, 2024
PDUFA:	April 14, 2024

❖ BACKGROUND:

Entresto is a combination of sacubitril and valsartan approved in 2015 to reduce the risk of cardiovascular (CV) death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction (HFrEF).

The favorable benefit-risk profile of Entresto for treatment of symptomatic heart failure (HF) with left ventricular systolic dysfunction (LVSD) in pediatric patients aged 1 year and older was previously established in 2019 (NDA 207620/S-013).

On April 20, 2020, Novartis submitted supplement which provided provides for updates to the United States Prescribing Information (USPI) and the Patient Package Insert (PPI) related to the PARAGON-HF trial, including substantive revisions to Indications and Usage and Clinical Studies; additional revisions were made throughout labeling.

Novartis Pharmaceuticals Corporation (the Applicant) has submitted a New Drug Application (NDA) for a new oral formulation of Entresto. The Dosage form is as film-coated granules with 2 dosage strengths, 6 mg/6 mg (4 film-coated granules) and 15 mg/16 mg (10 film-coated

granules), for an indication in the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older. The Applicant intents is to market this formulation under the same brand name as oral formulation film-coated tablets, Entresto®. In parallel with this NDA, Novartis also submitted a supplement to NDA 207620 to update the PI o based on the final efficacy and safety results of the pivotal clinical trial. Changes in labeling are reflected in the enclosed labeling.

- **REVIEW TEAM:**

  Jordan Pomeroy, MD, PhD, Clinical reviewer DCN
  Fortunato Senatore, MD, PhD, Clinical Team Leader, DCN
  Mary Ross Southworth, PharmD, Deputy Director for Safety, DCN
  Michael Monteleone, MS, RAC, Associate Director for Safety, DCN
  Theodor Carver, PhD, CMC Application Technical Leader, OPQ
  Nounou Mohammad, PhD, Clinical Pharmacology Reviewer, OCP
  Yuan Ye, PhD, Pharmacometrics reviewer, OCP
  Doanh, Tran, PhD, Deputy Director, OCP
  Meena Savani, PharmD, OPDP
  Lauri Buonaccorsi, PharmD, PLT Reviewer
  Amy Taylor, MD, DPMH Reviewer
  Shetarra Walker, MD, DPMH Team Leader
  Narendranath Reddy Chintagari, PhD, Non-Clinical
  Jean Wu, PhD, Non-Clinical supervisor
  Christina Topper, PharmD, DMEPA Reviewer
  Nicole Iverson, Pharm D, DMEPA Team Leader

- **LABELING:**

Labeling discussions occurred with the applicant. Applicant submitted the final agreed upon labeling on April 9, 2024.

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MARYAM CHANGI
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MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	April 8, 2024
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 218591 and NDA 207620/S-025
Product Name, Dosage Form, and Strength:	Entresto Sprinkle (sacubitril and valsartan) oral pellets, 6 mg/6 mg (proposed) and 15 mg/16 mg (proposed) Entresto (sacubitril and valsartan) tablets, 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg
Applicant Name:	Novartis Pharmaceuticals Corporation (Novartis)
FDA Received Date:	April 5, 2024
TTT ID #:	2023-5243-1 and 2023-6590-1
DMEPA 2 Team Leader (Acting):	Nicole Iverson, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

Novartis Pharmaceuticals Corporation (Novartis) submitted revised container labels received on April 5, 2024 for Entresto Sprinkle. We reviewed the revised container labels for Entresto Sprinkle (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

Novartis Pharmaceuticals Corporation (Novartis) implemented all of our recommendations and we have no additional recommendations at this time.

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[a] Iverson, N. Label and Labeling Review for Entresto Sprinkle (NDA 218591 and NDA 207620/S-025). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 MAR 19. TTT ID: 2023-5243-1 and 2023-6590-1.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: April 1, 2024

To: Maryam Changi, Regulatory Project Manager
Division of Cardiology and Nephrology (DCN)

Michael Monteleone, MS, RAC
Associate Director for Labeling, DCN

From: Meena Savani, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sapna Shah, MPH, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for ENTRESTO SPRINKLE (sacubitril and valsartan) granules and ENTRESTO (sacubitril and valsartan) tablets

NDA: NDA 207620 S-025
NDA 218591

Background:
In response to DCN's consult request dated July 26, 2024, OPDP has reviewed the proposed Entresto/Entresto Sprinkle Prescribing Information (PI) and Patient Package Insert (PPI) as well as the Entresto Sprinkle Instructions for Use (IFU) for Entresto supplement 025 and for the Entresto Sprinkle original NDA. This original NDA for Entresto Sprinkle proposes a new oral formulation of film-coated granules and S-025 proposes updates to the PI based on final efficacy and safety results for the PANORAMA-HF trial.

PI/PPI/IFU:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on March 28, 2024, and we do not have any comments at this time.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed PPI and IFU, and comments were sent under separate cover on March 29, 2024.

Thank you for your consult. If you have any questions, please contact Meena Savani at 240-402-1348 or Meena.Savani@fda.hhs.gov.

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/s/

MEENA R SAVANI
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	March 29, 2024
To:	Maryam Changi, PharmD Regulatory Project Manager **Division of Cardiology and Nephrology (DCN)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, WOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Laurie Buonaccorsi, PharmD Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Meena Savani, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (non-proprietary name), Dosage Form and Route, Application Type/ Number, Supplement Number:	• ENTRESTO SPRINKLE (sacubitril and valsartan) oral pellets, NDA 218591 • ENTRESTO (sacubitril and valsartan) tablets, for oral use, NDA 207620 S-025
Applicant:	Novartis Pharmaceuticals Corporation

1 INTRODUCTION

On June 14, 2023, Novartis Pharmaceuticals Corporation submitted for the Agency's review an original New Drug Application (NDA) 218591 for ENTRESTO SPRINKLE (sacubitril and valsartan), oral pellets, and a Prior Approval Supplement (PAS) – Efficacy to their approved NDA 207620/S-025 for ENTRESTO (sacubitril and valsartan) tablets. With these submissions, the Applicant proposes the following for the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older:

NDA 218591 ENTRESTO SPRINKLE

- a new oral formulation of film coated oral pellets within capsules with two dosage strengths.

NDA 207620/S-025 ENTRESTO

- to update the Prescribing Information (PI) based on final efficacy and safety pivotal study results (Study B2319) to support the approval of the pediatric indication.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to requests by the Division of Cardiology and Nephrology (DCN) on November 2, 2023 and July 26, 2023, respectively, to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for ENTRESTO SPRINKLE (sacubitril and valsartan) oral pellets and ENTRESTO (sacubitril and valsartan) tablets.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed on March 19, 2024.

2 MATERIAL REVIEWED

- Draft ENTRESTO SPRINKLE (sacubitril and valsartan) oral pellets and ENTRESTO (sacubitril and valsartan) tablets PPI received on June 14, 2023, and received by DMPP and OPDP on March 25, 2024, revised and received on March 28, 2024.
- Draft ENTRESTO SPRINKLE (sacubitril and valsartan) oral pellets IFU received on June 14, 2023, and received by DMPP and OPDP on March 25, 2024, revised and received on March 28, 2024.
- Draft ENTRESTO SPRINKLE (sacubitril and valsartan) oral pellets and ENTRESTO (sacubitril and valsartan) tablets PI received on June 14, 2023, revised throughout the review cycle, and received by DMPP and OPDP on March 25, 2024, further revised and received on March 28, 2024.
- Approved ENTRESTO (sacubitril and valsartan) tablets labeling dated February 16, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the IFU, the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the PI
- removed unnecessary or redundant information
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that they are free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the IFU meets the criteria as specified in both the FDA Guidance for Useful Written Consumer Medication Information (published July 2006) and Instructions for Use-Patient Labeling for Human Prescription Drug and Biological Products (published July 2022)

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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/s/

LAURIE J BUONACCORSI
03/29/2024 01:59:30 PM

MEENA R SAVANI
03/29/2024 02:23:37 PM

BARBARA A FULLER
03/29/2024 02:32:26 PM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

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Date of This Review:	March 19, 2024
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 218591 and NDA 207620/S-025
Product Name, Dosage Form, and Strength:	Entresto Sprinkle (sacubitril and valsartan) granules, 6 mg/6 mg (proposed) and 15 mg/16 mg (proposed) Entresto (sacubitril and valsartan) tablets, 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg
Product Type:	Multi-Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Novartis Pharmaceuticals Corporation (Novartis)
FDA Received Date:	June 14, 2023 and November 13, 2023
TTT ID #:	2023-5243 and 2023-6590
DMEPA 2 Safety Evaluator:	Christina Topper, PharmD, BCPS
DMEPA 2 Team Leader (Acting):	Nicole Iverson, PharmD, BCPS

1. REASON FOR REVIEW

Novartis Pharmaceuticals Corporation (Novartis) submitted an Efficacy Supplement for Entresto (sacubitril and valsartan) tablets (NDA 207620/S-025) to provide the final safety and efficacy data from the completed study CLCZ696B2319 (PANORAMA-HF).

In addition, a new presentation consisting of film-coated granules in capsules is proposed for registration under NDA 218591 in parallel to NDA 207620/S-025 to supplement the available extemporaneous suspension.

Subsequently, we reviewed the proposed Entresto prescribing information (PI), patient prescribing information (PPI), instructions for use (IFU) and container labels for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

Entresto (sacubitril and valsartan) tablets were approved under NDA 207620 on July 7, 2015 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. Entresto is currently available as 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg oral tablets. The proposed product under NDA 218591 is being developed as 6 mg/6 mg and 15 mg/16 mg oral granules in capsules (referred to as granules in the rest of the review).

2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3. OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed PI, PPI, IFU and container labels to determine if they are acceptable from a medication error perspective. We note the proposed product is packaged in a container/closure system that implies or affords a route of administration other

than the route intended. This may result in patients swallowing the capsules whole, rather than opening the capsules and sprinkling the contents on soft food as intended. On October 31, 2023, we sent an information request (IR) to Novartis recommending to conduct a risk analysis to identify and further evaluate hazards that may contribute to medication errors in addition to proposing risk-mitigation strategies and explaining how they plan to validate that the proposed strategies will address the identified risks and mitigate potential for errors. Novartis provided a response on November 13, 2023 indicating that the approved labeling for Entresto tablets was extensively updated with the addition of information related to Entresto granules to provide clear instructions for dosing and administration of granules packaged in capsules.

Currently the dosing of Entresto in pediatric patients is presented in a dosing table. With the introduction of the granules the existing dosing table introduces new concerns for calculating a dose. (b) (4) Prior to the introduction of the granule formulation, the labeling recommended use of the tablets to prepare an oral solution with a concentration of 4 mg/mL (sacubitril/valsartan 1.96/2.04 mg/mL) which is able to provide for exact weight-based doses. For example, a patient weighing 24 kg requiring a dose of 1.6 mg/kg would need 38.4 mg of the combined sacubitril/valsartan dosing and be able to use the 4 mg/mL oral solution to get the exact dose.

(b) (4)

As the granule formulation is only being proposed in two strengths, exact weight-based dosing would not be able to be achieved. Specifically, we are concerned with the lack of pre-calculated dose by weight that would require pharmacists to make decisions on how to round the dose to fit within the two proposed strengths of the granules. Additionally, this could result in calculation errors and in the use of a combination of the two proposed granule strengths to achieve certain doses increasing the potential of medication errors. Finally, we are concerned with the potential of an increased pill burden (b) (4) .

On December 7, 2023, we shared these concerns with the Division of Cardiology and Nephrology related to dosing confusion using the proposed Entresto granule formulation. The Division sent a second IR on January 4, 2024, requesting information related to mitigation strategies for potential dosing and administration errors associated with patients potentially requiring a combination of two proposed strengths to achieve a dose. On January 18, 2024 via

email correspondence, Novartis provided a response to the IR stating (b) (4) We disagreed with the Applicant's proposal and remained concerned that the proposed mitigations are not sufficient to mitigate the risk of dosing and administration errors.

To address these concerns, we obtained information from the Office of Clinical Pharmacology (OCP), to assist in defining the clinically safe and appropriate dosing variance intervals. Using the allowable variances provided by OCP, we developed a simplified dosing table for the proposed granules to help provide further guidance to prescribers on dosing and administration of the granule formulation in efforts to mitigate medication errors associated with wrong dosing and administration (see Appendix E). Specifically, the dosing table 1) provides a pre-calculated dose by weight, 2) eliminates the need for rounding decision by pharmacists, 3) mitigates calculation errors, 4) ensures use of a single strength of the granules, and 5) avoids unreasonable pill burden. We provided a draft of the dosing table to the review team, however, the Division did not agree that a dosing table for prescribers was necessary in the PI. We maintain our position that section 2.3 of the labeling is vulnerable to medication error. We find the dosing is complex and we recommend a dosing table is included to minimize the likelihood of medication error (b) (4) (b) (4). See Appendix E for the details of the IR's and see Section 4 for the dosing table proposed by DMEPA. As currently presented the proposed dosing table described dosing for pediatric patients (b) (4). Further discussion with OCP is warranted for doing of pediatric patients (b) (4). If the Division intends to proceed without the DMEPA drafted dosing table, we strongly recommend the labeling is revised such that only one strength of the capsule granule formulation should be used to achieve the intended dose (e.g. For granule administration, use one granule strength to achieve the dose) to reduce the potential of medication errors.

We note that both the tablet presentation (NDA 207620) and the granule presentation (NDA 218591) will be in the same PI. As such, the Highlights of Prescribing Information (Dosage and Administration and Dosage Forms and Strengths sections) were updated to add the proposed new dosage form. Section 2 (Dosage and Administration) was revised to add the proposed new dosage and administration sub-section for the administration of film-coated granules. Section 3 (Dosage Forms and Strengths) was revised to add information on how the film-coated granules appear and are supplied. Section 11 was revised to add the proposed film-coated granules description. Section 16 was revised to add the proposed film-coated granules description and packaging components in addition to formatting revisions. Section 17 was revised to add the administration instructions for the film-coated granules in line with the proposals in the PPI and IFU. The PPI was updated to add the administration instructions and inactive ingredients for the film-coated granules. The IFU was created for the addition of a new proposed formulation to facilitate the administration of the film-coated granules.

We note that the Office of Pharmaceutical Quality (OPQ) is still determining the appropriate dosage form for this proposed product. We identified areas of the proposed PI and container labels that could be revised to improve clarity, readability and availability of important information. For the Division, we recommend adding clarifying statements regarding dosage

and administration of the granule formulation, including the unit of measurement following each numeric value in the dosage and strength statements and removing the statement in the IFU [redacted] For the Applicant, we note the strength is not expressed by each ingredient, the placeholder for the lot number, expiration date, barcode, and product identifiers are missing, missing administration instructions, inconsistent terminology and increased prominence of the "Rx only" and net quantity statements.

4. CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed PI and container labels can be improved to promote the safe use of the product. We provide our recommendations in Section 4.1 for the Division and Section 4.2 for the Applicant below.

4.1 RECOMMENDATIONS FOR DIVISION OF CARDIOLOGY AND NEPHROLOGY (DCN)

A. Highlights of Prescribing Information (HPI) and Prescribing Information

1. As currently presented, the proprietary name for the granule formulation is denoted by the "Entresto". We reference our February 26, 2024 Proprietary Name Request Conditionally Acceptable letter informing you that the proprietary name, Entresto Sprinkle, was found conditionally acceptable for sacubitril/valsartan granules. We recommend replacing the name "Entresto" with the conditionally acceptable proprietary name, Entresto Sprinkle, for the granules formulation in your labeling.

B. Highlights of Prescribing Information (HPI)

1. Dosage and Administration

a. [redacted]

b. As currently presented the recommended starting dose for adults is missing. Lack of this information may lead medication dosing errors. We recommend including the statement as the first bullet, "The recommended starting dose for adults is 49/51 mg orally twice-daily." Additionally, we recommend bulleting the statement, "Adjust adult doses every 2 to 4 weeks [redacted] to the target maintenance dose, as tolerated by the patient. (2.2, [redacted]" for added clarity.

c. To increase availability of important information, we recommend adding the statement "For pediatric patients, see the Full Prescribing Information for recommended dosage, titrations, preparation and administration instructions. (2.3, 2.4, 2.5)" after the last bullet.

C. Prescribing Information

1. Dosage and Administration

a. As currently presented, the unit of measurement (e.g., mg) does not follow each numeric value in the strength statement. This may lead to confusion and potential risk of wrong dose error. We recommend ensuring the unit of measure follows each numeric value in the strength statement (e.g., 24 mg/26 mg, 49 mg/51 mg, 72 mg/78 mg, 97 mg/103 mg).

b. As currently presented the dosing with the proposed granule formulation is vulnerable to medication errors as the dosing is complex and we recommend the following dosing table be included in Section 2 of the PI.

Table 2: Recommended Dose Titration for Pediatric Patients using Granules†

	Titration Step Dose (twice daily)		
	Starting	Second	Final
Less than or equal to 13 kg	1.6 mg/kg‡	2.3 mg/kg‡	3.1 mg/kg‡
14 kg to 19 kg	12 mg/12 mg (Two 6 mg/6 mg granules)	18 mg/18 mg (Three 6 mg/6 mg granules)	24 mg/24 mg (Four 6 mg/6 mg granules)
20 kg to 26 kg	18 mg/18 mg (Three 6 mg/6 mg granules)	24 mg/24 mg (Four 6 mg/6 mg granules)	30 mg/32 mg (Two 15 mg/16 mg granules)
27 kg to 33 kg	24 mg/24 mg (Four 6 mg/6 mg granules)	30 mg/32 mg (Two 15 mg/16 mg granules)	45 mg/48 mg (Three 15 mg/16 mg granules)
34 kg to (b) (4) kg	30 mg/32 mg (Two 15 mg/16 mg granules)	45 mg/48 mg (Three 15 mg/16 mg granules)	60 mg/64 mg (Four 15 mg/16 mg granules)

† When using granules, more than one granule may be needed to achieve recommended doses.
‡ Use of the oral suspension is recommended in pediatric patients less than or equal to 13 kg. Recommended mg/kg doses are of the combined amount of both sacubitril and valsartan.

c. The title of Section 2.5 (b) (4) is misleading as it contains preparation and instructions of the granules. This may result in preparation errors if users are not aware that preparation information is also contained in Section 2.5. We recommend revising the title of Section 2.5 from (b) (4) to "Preparation and Administration of Oral Granules.".

d. In Section 2.5, we recommend adding the statement "Entresto Sprinkle are granules are contained within capsules." for added clarity.

e. [redacted]

f. For consistency with Section 17, Patient Information, and IFU, we recommend revising the statement in Section 2.5 "[redacted]" to read "Do not swallow the capsules. Do not chew or crush the granules.".

g. As currently presented in Section 2.6, 2.7. and 2.8, the unit of measurement (e.g., kg) does not follow each numeric value in the weight-based dosing statement. This may lead to confusion and potential risk of wrong dose error. We recommend adding the unit of measure following each numeric value (i.e. 40 kg to 50 kg).

2. Dosage Forms and Strengths

a. As currently presented, the unit of measurement (e.g., mg) does not follow each numeric value in the strength statement. This may lead to confusion and potential risk of wrong dose error. We recommend ensuring the unit of measure follows each numeric value in the strength statement (e.g., 24 mg/26 mg, 49 mg/51 mg, 97 mg/103 mg).

D. Instruction for Use (IFU)

1. Important Information You Need to Know Before Taking ENTRESTO Granules

a. For added clarity, we recommend adding the statement "Do NOT chew or crush the granules in the capsule".

b. We recommend removing the statement "[redacted]

c. We recommend removing the statement, "[redacted]

4.2 RECOMMENDATIONS FOR NOVARTIS PHARMACEUTICALS CORPORATION (NOVARTIS)

We recommend the following be implemented prior to approval of this NDA:

A. Container Labels

1. As currently presented, the proprietary name for the granules formulation is denoted by the "Entresto". We reference our February 26, 2024 Proprietary Name Request Conditionally Acceptable letter informing you that the proprietary name, Entresto Sprinkle, was found conditionally acceptable for sacubitril/valsartan granules. We recommend replacing the name "Entresto" with the conditionally acceptable proprietary name, Entresto Sprinkle, for the granules formulation and use the intend-to-market presentation of the proprietary name (font, color, etc.) so that we may adequately evaluate your labels and labeling.
2. As currently presented, there is a lack of adequate spacing between the numerical dose and unit of measure (e.g., 6mg/6mg and 15mg/16mg). Lack of adequate spacing may impact readability and might result in wrong strength errors. For example (e.g., the "m" in mg can sometimes be mistaken as a zero or two zeros). To improve readability, we recommend placing adequate space between the numerical dose and unit of measure (e.g., 6 mg/6 mg instead of 6mg/6mg and 15 mg/16 mg instead of 15mg/16mg).
3. The placeholder for the lot number is missing. Lot number statement is required on the immediate container AND carton labeling when there is sufficient space per 21 CFR 201.10(i)(1). We recommend adding the placeholder for the lot number in accordance 21 CFR 201.10(i)(1).
4. The placeholder for the expiration date is missing. The label of an official drug product shall bear an expiration date per USP General Chapter <7>. We recommend adding the placeholder for the expiration date in accordance with USP General Chapter <7>. We recommend you ensure that there are no other numbers located in close proximity to the expiration date. To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend identifying the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash to separate the portions of the expiration date.
5. The product identifier is missing. In June 2021, FDA finalized the Guidance for Industry on product identifiers required under the Drug Supply Chain Security Act (DSCSA). The Act requires manufacturers and re-packagers to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce. The product identifier includes the NDC, serial number, lot number, and expiration date in

both a human-readable form and machine-readable (2D data matrix barcode) format. We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling. See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021). If you determine that the product identifier requirements apply to your product's labeling, we request you add a place holder to the carton labeling.

6. The linear barcode is missing on the container labels. The drug barcode is often used as an additional verification during the medication use process; therefore, it is an important safety feature that should be part of the label and is a requirement per 21 CFR 201.25(c)(2). Add the product's linear barcode to each individual container label and carton labeling in accordance with 21CFR 201.25(c)(2). The barcode should be placed in a conspicuous location where it will not be difficult to read because of distorted text. Additionally, the barcode should be placed in an area where it will not be damaged because it appears at the point of label separation (e.g., perforation).
7. The container label does not have instructions on how to properly administer the proposed product. Not including the correct administration method on the container labels and carton labeling may lead to wrong route of administration errors. *See Guidance for Industry: Safety Considerations for Product Design to Minimize Medication Errors (April 2016).* We recommend revising the container label to instruct users on how to properly administer sacubitril/valsartan. For example, "Capsules must be opened prior to ingestion. Do Not swallow capsules.."
8. "The terminology within the statement of dosage (i.e., (b) (4) is inconsistent with the terminology in the Prescribing Information. To ensure consistency with the terminology in the Prescribing Information, we recommend revising the statement of dosage to read, "Recommended Dosage: see Prescribing Information."
9. The "Rx only" statement appears more prominent than other critical information (e.g. established name, strength, dosage form) on the principal display panel. The "Rx only" statement should not compete in size and prominence with critical information on the principal display panel. We recommend the "Rx only" statement does not compete in size or prominence with critical information on the principal display panel. *See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).*
10. As currently presented, the net quantity statement is prominent. Product selection or dosing errors can occur if the net quantity statement is mistaken for the product strength, leading to [under- or over-dosing]. We recommend decreasing the prominence of the net quantity statement.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Entresto received on June 14, 2023 from Novartis Pharmaceuticals Corporation (Novartis).

Table 2. Relevant Product Information for Entresto	
Initial Approval Date	July 7, 2015
Active Ingredient	sacubitril and valsartan
Indication	• 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. • 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.
Route of Administration	Oral
Dosage Form	granules (***proposed***) and tablets
Strength	Tablets: 24 mg/26 mg; 49 mg/51 mg; 97 mg/103 mg Oral granules ***(proposed):*** 6 mg/6 mg and 15 mg/16 mg
Dose and Frequency	**Adult Heart Failure:** • The recommended starting dose of Entresto is 49 mg/51 mg twice daily. • Double the dose of Entresto after 2 to 4 weeks to target maintenance dose of 97 mg/103 mg twice daily, as tolerated by the patient. (b) (4) **Pediatric Heart Failure:** (b) (4)

<table>
<tr><td></td><td>(b) (4)

• Reduce starting dose to half the usually recommended dose for:
○ patients not currently taking an ACE inhibitor or ARB or previously taking a low dose of these agents
○ patients with severe renal impairment
○ patients with moderate hepatic impairment

Note: Initiate pediatric patients weighing 40 to 50 kg who meet the above criterion at 0.8 mg/kg twice daily using the oral suspension or granules</td></tr>
<tr><td>How Supplied</td><td>• ENTRESTO (sacubitril/valsartan) is available as unscored, ovaloid, biconvex, film-coated tablets, containing 24 mg of sacubitril and 26 mg of valsartan; 49 mg of sacubitril and 51 mg of valsartan; and 97 mg of sacubitril and 103 mg of valsartan.
• ENTRESTO film-coated granules are round, biconvex in shape. Granules in capsules are available in two strengths, one containing a total of 6 mg of sacubitril and 6 mg of valsartan; and another containing a total of 15 mg of sacubitril and 16 mg of valsartan. Granules are provided in a hard capsule which must be opened prior to administration.
<table>
<tr><td colspan="5">Sacubitril/Valsartan tablets</td></tr>
<tr><td>Strength</td><td>Color</td><td>Debossment</td><td colspan="2">NDC 0078-XXXX-XX</td></tr>
<tr><td colspan="3"></td><td>Bottle of 60</td><td>Bottle of 180</td></tr>
<tr><td>24 mg/26 mg</td><td>Violet white</td><td>“NVR” on one side and “LZ” on the other side</td><td>0659-20</td><td>0659-67</td></tr>
<tr><td>49 mg/51 mg</td><td>Pale yellow</td><td>“NVR” on one side and “L1” on the other side</td><td>0777-20</td><td>0777-67</td></tr>
<tr><td>97 mg/103 mg</td><td>Light pink</td><td>“NVR” on one side and “L11” on the other side</td><td>0696-20</td><td>0696-67</td></tr>
<tr><td colspan="5">Sacubitril/Valsartan granules</td></tr>
<tr><td>Strength</td><td>Color</td><td>Print</td><td colspan="2">NDC 0078-XXXX-XX</td></tr>
<tr><td colspan="3"></td><td>Bottle of 60</td><td></td></tr>
<tr><td>6 mg/6 mg</td><td>White cap and transparent body</td><td>“NVR” on the body, “04” on the cap and both parts with arrows</td><td>XXXX-XX</td><td></td></tr>
<tr><td>15 mg/16 mg</td><td>Yellow cap and transparent body</td><td>“NVR” on the body, “10” on the cap and both parts with arrows</td><td>XXXX-XX</td><td></td></tr>
</table></td></tr>
<tr><td>Storage</td><td>Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]. Protect from moisture.</td></tr>
</table>

APPENDIX B. PREVIOUS DMEPA REVIEWS

On September 18, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, "Entresto" and "NDA 207620" and "NDA 218591". Our search identified three previous reviews[a,b,c], and we considered our previous recommendations to see if they are applicable for this current review.

[a] Stewart, J. Label and Labeling Review for Entresto (NDA 207620). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 JUN 1. OSE RCM No.: 2015-233.

[b] Thomas, S. Label and Labeling Review Memo for Entresto (NDA 207620/S-13). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 SEP 13. OSE RCM No.: 2019-711-1.

[c] Thomas, S. Label and Labeling Review for Entresto (NDA 207620/S-16). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 NOV 15. OSE RCM No.: 2019-1774.

APPENDIX E. INFORMATION REQUESTS

FDA Information Request

On October 31, 2023, DMEPA submitted an information request to the Applicant regarding the proposed product's container closure system and information to address our medication error concerns.

> "We refer to your Request for Proprietary Name Review received on September 22, 2023 for NDA 218591 Entresto. We are reviewing your submission and have the following information request regarding the proposed product container closure system.
>
> We note the drug product is packaged in a container/closure system that implies or affords a route of administration other than the route intended. Use of a container/closure system that implies or affords a route of administration other than the route intended may result in wrong route or wrong administration technique.
>
> We have determined that the introduction of your proposed container/closure system for Entresto would increase the potential for wrong route of administration errors because the drug product is packaged in a container/closure system that implies or affords a route of administration other than the route intended. This may result in patients swallowing the capsules whole, rather than opening the capsules and sprinkling the contents on soft food as intended.
>
> We recommend you conduct a risk analysis to identify and further evaluate hazards that may contribute to medication errors. Please propose risk-mitigation strategies and explain how you plan to validate that your proposed strategies will address the identified risks and mitigate the potential for errors."

Applicant Response Received on November 13, 2023:

\\CDSESUB1\EVSPROD\nda218591\0007\m1\us\fda-response-clinical.pdf

FDA Information Request

On January 4, 2024, the Division and DMEPA submitted an information request to the Applicant regarding dosing using the granules [redacted] (b) (4)

> *Section 2.3 of your proposed label states,* [redacted] (b) (4) *We do not consider this comment in section 2.3 as final. We are concerned that your new Entresto granule formulation will not provide accurate dosing for pediatric patients* [redacted] (b) (4) *Please provide evidence to justify that the Entresto granule formulation (NDA 218591) will provide accurate dosing for pediatric patients* [redacted] (b) (4) *or provide additional guidance for appropriate weight groups in which your Entresto granule formulation is appropriate. Also, please provide*

information on whether the Entresto granule formulation would be considered a substitute for an oral suspension. Additionally, we have the following questions:

a. *Are individual Entresto granules suitable for manipulation to facilitate lower doses, and can dose accuracy and uniformity be achieved using the individual granules/minitablets?*

b. *Do you have available dissolution and stability data for your Entresto granule formulation in an oral suspension?*

2. *We noted that certain recommended doses (e.g., (b) (4) We are concerned that the (b) (4) may be prone to medication dosing and administration errors. Do you intend on patients (b) (4) or use the suspension formulation? If the intent is for patients to be (b) (4) how do you intend to mitigate dosing and administration errors?*

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[d] along with postmarket medication error data, we reviewed the following Entresto labels and labeling submitted by Novartis Pharmaceuticals Corporation (Novartis).

- Container labels received on November 28, 2023
- Prescribing Information, Patient Prescribing Information and Instructions for Use (Image not shown) received on June 14, 2023 and November 28, 2023, available from
  - \\CDSESUB1\EVSPROD\nda207620\0188\m1\us\proposed-clean.pdf
  - \\CDSESUB1\EVSPROD\nda218591\0009\m1\us\proposed.pdf

F.2 Label and Labeling Images

1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[d] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/

NICOLE F IVERSON on behalf of CHRISTINA A TOPPER
03/19/2024 08:23:10 AM

NICOLE F IVERSON
03/19/2024 08:24:45 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic
and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

PLLR Labeling Memorandum

Date: 12/11/2023 **Date consulted:** 7/14/2023

From: Katherine Kratz, MD, Medical Officer, Maternal Health, Division of Pediatrics and Maternal Health (DPMH)

Through: Miriam Dinatale, DO, Team Leader, Maternal Health, DPMH

Lynne P. Yao, MD, OND, Division Director, DPMH

To: Division of Cardiology and Nephrology (DCN)

Drug: ENTRESTO (sacubitril/valsartan) film-coated granules

NDAs: 218591 and 207620/S-025

Applicant: Novartis Pharmaceuticals Corporation

Subject: Pregnancy and Lactation Labeling

Proposed Indication:

For the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older

Materials Reviewed:

- DPMH consult request dated 7/14/2023. DARRTS Reference ID: 5209504.
- Applicant's submitted background package and proposed labeling for NDA 218591 sequence number (SN) 0000 and 207620 SN 0188 submitted 6/14/2023.

- NDA 207620 Periodic Safety Update Report (PSUR): Period covered 8/1/2022-7/31/2023. SN 0196. Submitted 10/5/2023.
- NDA 207620 Periodic Safety Update Report (PSUR): Period covered 8/1/2021-7/31/2022. SN 0185. Submitted 10/3/2022.
- NDA 207620 Periodic Safety Update Report (PSUR): Period covered 8/1/2020-7/31/2021. SN 0172. Submitted 10/6/2021.
- NDA 207620 Periodic Safety Update Report (PSUR): Period covered 8/1/2019-7/31/2020. SN 0156. Submitted 10/6/2020.
- NDA 207620 Periodic Safety Update Report (PSUR): Period covered 8/1/2018-7/31/2019. SN 0134. Submitted 10/7/2019.
- NDA 207620 Periodic Safety Update Report (PSUR): Period covered 2/1/2018-7/31/2018. SN 0110. Submitted 9/27/2018.
- NDA 207620 Periodic Safety Update Report (PSUR): Period covered 8/1/2017-1/31/2018. SN 0099. Submitted 4/5/2018.
- NDA 207620 Periodic Safety Update Report (PSUR): Period covered 7/7/2016-1/31/2017. SN 0086. Submitted 3/27/2017.
- DPMH Memorandum for LCZ696 (sacubitril/valsartan) tablets, NDA 207620, by Miriam Dinatale, DO, dated 5/26/2015. DARRTS Reference ID: 3764048.
- United States Prescribing Information (USPI) for ENTRESTO. Revised 2/2021.

Consult Request: "Provide comments on labeling and attend meetings if needed."

INTRODUCTION

On June 14, 2023, Novartis Pharmaceuticals Corporation submitted a new drug application (NDA) and a prior approval efficacy supplement for ENTRESTO (sacubitril/valsartan) seeking approval of a new formulation (film-coated granules) for the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older. DCN consulted the DPMH Maternal Health Team (MHT) on July 14, 2023 to assist with the Pregnancy and Lactation subsections of labeling. The Applicant is not proposing any changes to the labeling related to pregnancy and lactation.

BACKGROUND

- July 2015: Entresto (tablets) was approved 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 in the formulation of film-coated tablets.
- DPMH was consulted to review Entresto during the initial review cycle.[1] The reader is referred to the 2015 DPMH consult for the background on Entresto.
- October 2019: Entresto was approved for the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older.

[1] DPMH Memorandum for LCZ696 (sacubitril/valsartan) tablets, NDA 207620, by Miriam Dinatale, DO, dated 5/26/2015. DARRTS Reference ID: 3764048.

- The USPI for Entresto is in the Pregnancy and Lactation Labeling Rule (PLLR) format and contains a boxed warning for fetal toxicity, as drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus. The USPI also states that breastfeeding is not recommended.

DATA REVIEW

No new nonclinical data related to pregnancy or lactation were provided by the Applicant for NDA 218591 or for sNDA 207620.

In the most recent PSUR for NDA 207620,[2] thirty-seven cases of maternal exposure during pregnancy and four cases of maternal exposure during breastfeeding are listed in the "Cumulative and interval summary tabulations of serious and non-serious adverse reactions from post-marketing data sources." By reviewing the PSURs submitted by the Applicant after approval from March 2017 through July 2023, DPMH was able to create tables of the post-marketing cases of maternal exposure during pregnancy (Appendix A) and of cases of maternal exposure during breastfeeding (Appendix B). As shown in Appendix A, data are missing for most patients on timing of exposure and pregnancy outcome. As shown in Appendix B, timing of exposure during lactation and outcomes are missing. According to the Applicant, the evaluation of all cases did not provide any new or unknown safety finding.

> ***Reviewer comment:***
> *It is notable that there were 37 exposures in pregnancy, which is a substantive number for a drug that contains a boxed warning for embryofetal toxicity. After DPMH's review of the PSURs, DPMH concurs with the applicant that the cases of maternal exposure during pregnancy and lactation did not provide new safety findings. Without timing of exposure and outcome data, the data are not useful. There were only 4 patient exposures during lactation, and the data for these cases were also limited, and therefore, not useful in evaluating for risks associated with lactation. DPMH discussed issuing a descriptive pregnancy safety study (DPSS) with DCN as a means for having a structured approach for data collection to obtain follow-up information on all exposed pregnancies of which the Applicant becomes aware. Given that the safety risks associated with ARBs and pregnancy are well-described, DCN did not support issuing a DPSS. Although the safety risks associated with ARB use in pregnancy are well-characterized, there is limited information on sacubitril use during pregnancy. Thus, DPMH continues to recommend a structured approach to pregnancy data collection through a DPSS. See the Discussion and Conclusions section below for more information about labeling recommendations and a DPSS.*

Under NDA 218591, there were no pregnancies or exposures via breastmilk reported in the clinical trials conducted to establish efficacy in the pediatric population.

[2] NDA 207620 Periodic Safety Update Report (PSUR): Period covered 8/1/2022-7/31/2023. Submitted 10/5/2023.

The Applicant stated that "No new safety information emerged from the review of the literature related to this topic."

DPMH conducted a search of published human studies related to sacubitril and/or valsartan and pregnancy, lactation and fertility in PubMed from 2015 (date of last DPMH MHT review) to the present. The following search terms were used: "sacubitril" OR "valsartan" OR "sacubitril and valsartan" OR "Entresto" and "pregnancy," "pregnancy outcomes," "birth defects," "malformations," "stillbirth," "spontaneous abortion," "lactation," "breastfeeding," "fertility," "contraception," "oral contraceptives," and "infertility." The DPMH MHT review team identified the following case reports related to peripartum use of Entresto and a valsartan-containing drug product:

- A 24-year-old female at 17 weeks and 3 days of gestation presented with new onset biventricular heart failure (i.e., pregnancy-associated cardiomyopathy) and was treated with furosemide, hydralazine, isosorbide dinitrate, and carvedilol during pregnancy.[3] Postpartum, she had refractory symptoms of heart failure and treatment with Entresto was started. There was no fetal exposure to Entresto during pregnancy, and the case report did not indicate whether the patient breastfed the infant during treatment with Entresto. No new information related to Entresto use during pregnancy and/or lactation was obtained from this case report.

- A 39-year-old female at 30 weeks of gestation underwent a routine ultrasound and anhydramnios was noted.[4] On ultrasound, the fetal bladder was not visualized, and the kidneys appeared to be of normal size and echogenicity. Preterm premature rupture of membranes was ruled out. The patient was taking Codiovan (valsartan 160mg + hydrochlorothiazide 12.5mg) daily for treatment of essential hypertension, which had been started 3 years prior to the pregnancy. Codiovan treatment was stopped. Two weeks later, a follow-up fetal ultrasound showed a normal amniotic fluid index and normal bladder and kidneys.

DPMH also searched Micromedex,[5] Reprotox,[6] TERIS,[7] Shepard's,[8] Hale's *Medications and Mothers' Milk*,[9] the Drugs and Lactation Database (LactMed),[10] and Briggs *Drugs in*

[3] Gaddipati VC, Patel AA, Cohen AJ. The Use of a Novel Heart Failure Agent in the Treatment of Pregnancy-Associated Cardiomyopathy. Case Rep Cardiol. 2017;2017:9561405. doi: 10.1155/2017/9561405. Epub 2017 Aug 14. PMID: 28890834; PMCID: PMC5584348.
[4] Saar T, Levitt L, Amsalem H. Reversible Fetal Renal Impairment following Angiotensin Receptor Blocking Treatment during Third Trimester of Pregnancy: Case Report and Review of the Literature. Case Rep Obstet Gynecol. 2016;2016:2382031. doi: 10.1155/2016/2382031. Epub 2016 Sep 8. PMID: 27672462; PMCID: PMC5031874.
[5] Truven Health Analytics information, http://www.micromedexsolutions.com. Accessed 8/3/22.
[6] Reprotox Website: www.Reprotox.org. Accessed 8/3/22.
[7] TERIS database, Truven Health Analytics, Micromedex Solutions. Accessed 8/4/22.
[8] Shepard's database, Truven Health Analytics, Micromedex Solutions. Accessed 8/3/22.
[9] Hale, Thomas W. Hale's Medications & Mothers' Milk 2021: A Manual of Lactational Pharmacology. 19th ed. New York: Springer Publishing Company, 2020. www.halesmeds.com
[10] Drugs and Lactation Database (LactMed). Accessed 7/26/22.

Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk.[11] No new information was identified in these sources.

Reviewer comment:
The published case reports do not provide new information to inform labeling.

DISCUSSION/CONCLUSIONS

There are no new data pertaining to pregnancy, lactation or reproduction to include in labeling. DPMH MHT recommends making minor changes to the labeling. Given the large number of pregnancy exposures reported to the Applicant's pharmacovigilance database since Entresto approval in 2015 and the lack of pregnancy outcome data, DPMH recommends issuing a postmarketing requirement for a DPSS to collect pregnancy outcome data in a structured manner.

RECOMMENDATIONS

DPMH revised the Highlights of Prescribing Information, subsections 8.1 and 8.2, and section 17 (shown below). The existing labeling text appears in black. The recommended additions appear in blue. The text that DPMH MHT recommends removing contains a strikethrough. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

(b) (4)

[11] Briggs, Gerald G., Craig V. Towers, and Alicia B. Forinash. Briggs Drugs in Pregnancy and Lactation: a Reference Guide to Fetal and Neonatal Risk. 12th edition. Philadelphia, PA: Lippincott Williams & Wilkins, 2021. Print.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS)

Appendix A – Reviewer generated table of maternal exposures during pregnancy taken from PSURs between 7/2016-7/2023

#	Case ID Number	Exposure	Outcome	Sequence Number of PSUR
1	PHEH2016US017203	Unknown	Unknown	0086/0110
2	PHEH2017US003021	Unknown	Unknown	0086/0099
3	PHEH2017US024348	Unknown	Unknown	0099/0134
4	PHEH2017US035714	Unknown	Unknown	0099/0134
5	PHHY2017FR150038	Unknown	Unknown	0099/0134
6	PHEH2017US008012	Unknown	Unknown	0110
7	PHEH2018US034708	Unknown	Unknown	0134
8	PHEH2018US052746	Unknown	Unknown	0134
9	PHEH2018US056035	Unknown; stopped as soon as pregnant suspected	Unknown	0134
10	PHEH2019US003008	Unknown	Unknown	0134
11	PHEH2019US027199	At 22 weeks of gestation Took Entresto 200 mg TID x 4 days	Normal baby	0134/0156/0172
12	NVSC2019US012101	Unknown	Unknown	0156/0172
13	PHEH2019US003168	Unknown	Unknown	0156/0134
14	PHEH2019US024559	Unknown	Unknown	0134/0156/0172
15	PHEH2019US034573	Unknown	Unknown	0156
16	NVSC2020US089188	Unknown	Preterm delivery at 32 weeks	0156
17	NVSC2021US166601	Unknown	Unknown	0172
18	NVSC2020US143083	Unknown	Unknown	0172
19	NVSC2020HU311602	Unknown	Pre-eclampsia	0172
20	NVSC2021US077645	Unknown	Infant in NICU “left side of heart too small to pump”	0172/0185
21	NVSC2020GB241653	Unknown	Premature baby Fetal pulmonary hypoplasia/hypertension and renal failure Concomitant meds: nifedipine, atorvastatin, bisoprolol, and flutamide	0172
22	NVSC2020US178027	Unknown	Premature baby 33 weeks	0172/0185

23	NVSC2020US182785	Became pregnant in Oct and stopped taking in Nov	Premature baby	0172
24	NVSC2021US088802	Unknown Peripartum cardiomyopathy	Normal baby	0172/0185
25	NVSC2021US226428	Unknown	Normal baby	0185/0196
26	NVSC2022US017395	Unknown	Unknown	0185
27	NVSC2021US276001	Unknown	Unknown	0185
28	NVSC2021US294783	Unknown	Unknown	0185
29	NVSC2021US173598	Unknown Peripartum cardiomyopathy	Unknown	0185
30	NVSC2021CN222560	Unknown	Premature baby 32.6 weeks Exposed to sacubitril, valsartan, furosemide, torasemide, spironolactone, metoprolol	0185
31	NVSC2023US052770	Unknown	Unknown	0196
32	NVSC2022US179042	Unknown	Unknown	0196
33	NVSC2023US034553	Unknown	Unknown	0196
34	NVSC2023US158513	Unknown	Unknown	0196
35	NVSC2022PH186115	Unknown	Unknown	0196
36	NVSC2022US186648	Unknown	Oligohydramnios	0196
37	NVSC2022US186650	Chronic fetal exposure during pregnancy	Renal tubular dysplasia Hypocalvaria Pulmonary hypoplasia Neonatal death	0196

Appendix B – Reviewer generated table of maternal exposures during lactation taken from PSURs between 7/2016-7/2023

#	Case ID Number	Exposure	Outcome	Sequence Number of PSUR
1	Not provided	Unknown	Unknown	0134
2	NVSC2020GH291076 (mother)/ NVSC2020GH353672 (baby)	Treatment for postpartum dilated cardiomyopathy Infant exposed during lactation Unknown duration of exposure	"After exposure to Entresto, the baby experienced 'Rash', which is a listed event."	0172
3	NVSC2021KE129526	Treatment for heart failure (HF) at 50 mg qday Unknown duration of exposure	No adverse events	0172
	NVSJ2022JP095505	Unknown	Unknown	0196

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/

KATHERINE G KRATZ
12/11/2023 01:00:56 PM

MIRIAM C DINATALE
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LYNNE P YAO
12/11/2023 01:32:24 PM