

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
ANDA 213748

Name: Sacubitril and Valsartan Tablets; 24mg/26mg, 49mg/51mg,
and 97mg/103mg

Sponsor: MSN Pharmaceuticals Inc.

Approval Date: July 24, 2024

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 213748

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 213748

APPROVAL LETTER



ANDA 213748

ANDA APPROVAL

MSN Pharmaceuticals Inc.
U.S. Agent for MSN Laboratories Private Limited
20 Duke Road
Piscataway, NJ 08854-3714
Attention: Kondal Reddy Bairy
Vice President

Dear Kondal Reddy Bairy:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on July 8, 2019, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Sacubitril and Valsartan Tablets, 24 mg/26 mg, 49 mg /51 mg, and 97 mg/103 mg.

Reference is also made to the complete response letter issued by this office on March 22, 2024, and to any amendments thereafter.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug meets the requirements for approval under the FD&C Act. Accordingly, the ANDA is **approved**, effective on the date of this letter. We have determined your Sacubitril and Valsartan Tablets, 24 mg/26 mg, 49 mg /51 mg, and 97 mg/103 mg to be bioequivalent and therapeutically equivalent to the reference listed drug (RLD), Entresto Tablets, 24 mg/26 mg, 49 mg /51 mg, and 97 mg/103 mg, of Novartis Pharmaceuticals Corporation (Novartis).

The RLD upon which you have based your ANDA, Novartis's Entresto Tablets, 24 mg/26 mg, 49 mg /51 mg, and 97 mg/103 mg, is subject to periods of patent protection. The following patents and expiration dates are currently listed in the Agency's publication titled *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book"):

<u>U.S. Patent Number</u>	<u>Expiration Date</u>
8,101,659 (the '659 patent)	July 15, 2025*
8,877,938 (the '938 patent)	November 27, 2027*
9,388,134 (the '134 patent)	May 8, 2027*

9,517,226 (the '226 patent)	August 22, 2033
9,937,143 (the '143 patent)	August 22, 2033
11,058,667 (the '667 patent)	May 9, 2036
11,135,192 (the '192 patent)	August 22, 2033

* with pediatric exclusivity added

Your ANDA contains paragraph IV certifications to the '659, '938 and '134 patents, under section 505(j)(2)(A)(vii)(IV) of the FD&C Act stating that the patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Sacubitril and Valsartan Tablets, 24 mg/26 mg, 49 mg /51 mg, and 97 mg/103 mg, under this ANDA. You have notified the Agency that MSN Laboratories Private Limited (MSN) complied with the requirements of section 505(j)(2)(B) of the FD&C Act. Litigation was initiated within the statutory 45-day period against MSN for infringement of the '659, '938 and '134 patents in the United States District Court for the District of Delaware [Novartis Pharmaceuticals Corporation v. MSN Pharmaceuticals Inc., et al., Civil Action No. 19-02053]. The 8 year period identified in section 505(j)(5)(B)(iii) of the FD&C Act, during which FDA was precluded from approving your ANDA, has expired.

With respect to the '226, '143, '667 and '192 patents, your ANDA contains statements under section 505(j)(2)(A)(viii) of the FD&C Act that these are method-of-use patents that do not claim any indication or other conditions of use for which you are seeking approval under your ANDA.

With respect to 180-day generic drug exclusivity, we note that MSN was a first ANDA applicant for Sacubitril and Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg, to submit a substantially complete ANDA with a paragraph IV certification. Therefore, with this approval, MSN may be eligible for 180 days of generic drug exclusivity for Sacubitril and Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg. This exclusivity, which is provided for under 505(j)(5)(B)(iv) of the FD&C Act, would begin to run from the date of the commercial marketing identified in section 505(j)(5)(B)(iv). The Agency notes that MSN failed to obtain tentative approval of this ANDA within 30 months after the date of which the ANDA was filed. See section 505(j)(5)(D)(i)(IV) of the FD&C Act (forfeiture of exclusivity for failure to obtain tentative approval). The Agency is not, however, making a formal determination at this time of MSN's eligibility for 180-day generic drug exclusivity. We will do so only if a subsequent paragraph IV applicant becomes eligible for full approval (a) within 180 days after MSN begins commercial marketing of Sacubitril and Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg, or (b) at any time prior to the expiration of the '659, '938, and '134 patents if MSN has not begun commercial marketing. Please submit correspondence to this ANDA notifying the Agency within 30 days of the date of the first commercial marketing of this drug product or the RLD. If you do not notify the Agency within 30 days, the date of first commercial marketing will be deemed

to be the date of the drug product's approval. See 21 CFR 314.107(c)(2).

Please note that if FDA requires a Risk Evaluation and Mitigation Strategy (REMS) for a listed drug, an ANDA referencing that listed drug also will be required to have a REMS. See section 505-1(i) of the FD&C Act.

COMPENDIAL STANDARDS

A drug with a name recognized in the official United States Pharmacopeia or official National Formulary (USP-NF) generally must comply with the compendial standard for strength, quality, and purity, unless the difference in strength, quality, or purity is plainly stated on its label (see FD&C Act § 501(b), 21 USC 351(b)). FDA typically cannot share application-specific information contained in submitted regulatory filings with third parties, which includes USP-NF. To help ensure that a drug continues to comply with compendial standards, application holders may work directly with USP-NF to revise official USP monographs. More information on the USP-NF is available on USP's website as <https://www.uspnf.com/>.

REQUIREMENTS AND RECOMMENDATIONS POST APPROVAL

Under applicable statutes, regulations, and guidances, your ANDA may be subject to certain requirements and recommendations post approval, including requirements regarding changes to approved ANDAs, postmarketing reporting, promotional materials, and annual facility fees, among others. For information on post-approval requirements and recommendations for ANDAs and a list of resources for ANDA holders, we refer you to <https://www.fda.gov/drugs/abbreviated-new-drug-application-anda/requirements-and-resources-approved-andas>.

Sincerely yours,

{See appended electronic signature page}

For Edward M. Sherwood
Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research



Sarah
Kurtz



Digitally signed by Sarah Kurtz

Date: 7/24/2024 11:11:06AM

GUID: 54078879000a1b9e15dd31ed6f0343ca

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 213748

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all of the information needed to use SACUBITRIL AND VALSARTAN TABLETS safely and effectively. See full prescribing information for SACUBITRIL AND VALSARTAN TABLETS. SACUBITRIL AND VALSARTAN TABLETS, for oral use. Initial U.S. Approval: 2015

WARNING: FETAL TOXICITY	
• When pregnancy is detected, discontinue sacubitril and valsartan tablets as soon as possible (5.1). Drug that act directly on the renin-angiotensin system can cause injury and death to the developing fetus (5.1)	
RECENT MAJOR CHANGES	
• Dosage and Administration (2.3)	4/2024
INDICATIONS AND USAGE	
Sacubitril and valsartan tablets are a combination of sacubitril, a neprilysin inhibitor, and valsartan, an angiotensin II receptor blocker, and is indicated to:	
• to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure and reduced ejection fraction (1.1)	
• for the treatment of symptomatic heart failure with patients left ventricular ejection dysfunction in pediatric patients aged one year and older. Sacubitril and valsartan tablets reduces NT-proBNP and is expected to improve cardiovascular outcomes. (1.2)	
DOSEAGE AND ADMINISTRATION	
• The recommended starting dosage for adults is 49 mg/51 mg orally twice daily. The target maintenance dose is 97 mg/103 mg orally twice daily (2.2). Adjust adult dose every 2 to 4 weeks to the target maintenance dose, as tolerated by the patient (2.2)	
• For pediatric patients, see the Full Prescribing Information for recommended dosage, titration, preparation and administration instructions (2.3, 2.4)	
• Reduce starting dose to half the usually recommended starting dosage for: - o patients with severe renal impairment (2.7) - o patients with moderate hepatic impairment (2.8)	
DOSEAGE FORMS AND STRENGTHS	
• Film-coated tablets: 24/26 mg, 49/51 mg, 97/103 mg (3)	

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149. CLINICAL STUDIES

- This Patient Information has been approved by the U.S. Food and Drug Administration.
Issued on: 04/2024

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MSN

Each film-coated tablet contains 24 mg of sacubitril and 26 mg of valsartan.

Usual Dosage: See prescribing information

Store at 25°C (77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Protect from moisture.

Keep this and all drugs out of the reach of children.

M.L. No.: 5/MN/TS/2014/F/G

Manufactured by:
MSN Laboratories Private Limited
 Telangana- 509228,
 INDIA

Distributed by:
MSN Pharmaceuticals Inc.
 Piscataway, NJ 08854-3714

Issued: 10/2019
 DXXXX-XX

Rx Only

NDC 69539-166-60

Sacubitril and Valsartan
Tablets

24 mg/26 mg

MSN

60 Tablets

GTIN: XXXXXXXXXXXXXXXX

S.N: XXXXXXXXXXXXXXXX

EXP: MM/YYYY

LOT: XXXXXXXXXXXXXXXX

GTIN, S.N., EXP., & LOT, Details along with variable data shall be over coded with 2D during packing.

Coding area

(b)(4)



Each film-coated tablet contains 24 mg of sacubitril and 26 mg of valsartan.
 Usual Dosage: See prescribing information.
 Store at 25°C (77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].
 Protect from moisture.
 Keep this and all drugs out of the reach of children.
 M.L. No.: 5/MN/TS/2014/F/G
Manufactured by:
MSN Laboratories Private Limited
 Telangana - 509228,
 INDIA
Distributed by:
MSN Pharmaceuticals Inc.
 Piscataway, NJ 08854-3714
 Issued: 10/2019
 DXXXXXX-XX

Rx Only NDC 69539-166-18

Sacubitril and Valsartan
Tablets

24 mg/26 mg

MSN 180 Tablets



GTIN: XXXXXXXXXXXXXXXX
 S.N: XXXXXXXXXXXXXXXX
 EXP: MM/YYYY
 LOT: XXXXXXXXXXXXXXXX
 GTIN, S.N, EXP, & LOT: Details along with variable data shall be over coded with 2D during packing.

Coding area

(b)(4)

Each film-coated tablet contains 49 mg of sacubitril and 51 mg of valsartan.
 Usual Dosage: See prescribing information.
 Store at 25°C (77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].
 Protect from moisture.
 Keep this and all drugs out of the reach of children.

M.L. No.: 5/MN/TS/2014/F/G

Manufactured by:
MSN Laboratories Private Limited
 Telangana- 509228,
 INDIA

Distributed by:
MSN Pharmaceuticals Inc.
 Piscataway, NJ 08854-3714

Issued: 10/2019
 DXXXXX-XX

MSN

Rx Only NDC 69539-167-60

**Sacubitril and Valsartan
 Tablets**

49 mg/51 mg

60 Tablets



GTIN: XXXXXXXXXXXXXXXX
 S.N: XXXXXXXXXXXXXXXX
 EXP: MM/YYYY
 LOT: XXXXXXXXXXXXXXXX
 GTIN, S.N, EXP, & LOT, Details along with variable data shall be over coded with 2D during packing.

Coding area

(b)(4)



0 8 1 6 9 1 6 7 1 8 0

Each film-coated tablet contains 49 mg of sacubitril and 51 mg of valsartan. Usual Dosage: See prescribing information. Store at 25°C (77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from moisture. Keep this and all drugs out of the reach of children.

M.L. No.: 5/MN/TS/2014/F/G

Manufactured by:
MSN Laboratories Private Limited
Telangana - 509228,
INDIA

Distributed by:
MSN Pharmaceuticals Inc.
Piscataway, NJ 08854-3714

Issued: 10/2019
DXXXXXXX

Rx Only NDC 69539-167-18

**Sacubitril and Valsartan
Tablets**

49 mg/51 mg

MSN 180 Tablets



GTIN: XXXXXXXXXXXXX
S.N. XXXXXXXXXXXXXXX
EXP. MM/YYYY
LOT: XXXXXXXXXXXXX
GTIN, S.N., EXP. & LOT: Details along with variable data shall be over coded with 2D during packing.

Coding area

(b)(4)

Each film-coated tablet contains 97 mg of sacubitril and 103 mg of valsartan.
Usual Dosage: See prescribing information.
Store at 25°C (77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].
Protect from moisture.
Keep this and all drugs out of the reach of children.
M.L. No.: 5/MN/TS/2014/F/G
Manufactured by:
MSN Laboratories Private Limited
 Telangana- 509228,
 INDIA
Distributed by:
MSN Pharmaceuticals Inc.
 Piscataway, NJ 08854-3714
 Issued: 10/2019
 DXXXXXX

Rx Only **NDC 69539-168-60**

Sacubitril and Valsartan
Tablets
97 mg/103 mg

60 Tablets

OTIN: XXXXXXXXXXXXXXXX
 SN: XXXXXXXXXXXXXXXX
 EXP: MM/YYYY
 LOT: XXXXXXXXXX
 OTIN, SN, EXP, & LOT, Details along with variable data shall be over coded with 2D during pecking.

Coding area

(b)(4)



69539168187

Each film-coated tablet contains 97 mg of sacubitril and 103 mg of valsartan.
Usual Dosage: See prescribing information.
Store at 25°C (77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].
Protect from moisture.
Keep this and all drugs out of the reach of children.
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 INDIA
Distributed by:
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 Piscataway, NJ 08854-3714
 Issued: 10/2019
 DXXXXXX

Rx Only NDC 69539-168-18

Sacubitril and Valsartan
Tablets
97 mg/103 mg

MSN

180 Tablets



GTIN: XXXXXXXXXXXXXXXX
 S.N: XXXXXXXXXXXXXXXX
 EXP: MM/YYYY
 LOT: XXXXXXXXXXXXXXXX
 GTIN, S.N, EXP, & LOT, Details along with variable data shall be over coded with 2D during packing

Coding area

(b)(4)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 213748

LABELING REVIEW(s)

Labeling Review

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	July 16, 2024
ANDA Number(s)	213748
Review Number	7
Applicant Name	MSN Laboratories Private Limited
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Sacubitril and Valsartan Tablets, 24 mg/26 mg, 49 mg /51 mg, and 97 mg/103 mg
Proposed Proprietary Name	None
Submission Received Date	July 15, 2024
Primary Labeling Reviewer	Angela Payne, RPh
Secondary Labeling Reviewer	Refer to signature page
Review Conclusion ☒ Acceptable - No Comments ☐ Acceptable - Include Post Approval Comments ☐ Minor Deficiency* - Refer to Labeling Deficiencies and Comments for Letter to Applicant ☐ Major Deficiency** - Refer to Labeling Deficiencies and Comments for Letter to Applicant	
On Policy Alert List	☒ Yes ☐ No
Acceptable For Filing	☒ Yes ☐ No
Combined Insert/Outsert	☐ Yes ☒ No

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<u>5.3</u>	<u>PRESCRIBING INFORMATION</u>
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<u>6</u>	<u>COMMENTS/CONSULTS FOR OTHER DISCIPLINES</u>

1 **LABELING COMMENTS (C7)**

1.1 **LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT (C7)**

1.2 **COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE (C7)**

The Division of Labeling has no further questions/comments at this time based on your labeling submission received July 15, 2024.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book (OB), and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.3 **POST-APPROVAL REVISIONS (C7)**

These comments will be addressed post approval (in the first labeling supplement review).

2 **INSTRUCTIONS FOR ASSESSMENT (C7)**

General Comments:

Select the "no deficiency" or "deficiency" radio button as appropriate for each row. If a "Deficiency Comments" appears, ensure it is appropriate for your situation, edit, or enter "Reviewer Comments" if necessary.

If there is no issue/concern, or if the question is not applicable. No "Deficiency Comments" will appear but reviewers can still enter "Reviewer Comments" if desired.

☐	☒	There is information in the Orange Book that the applicant needs to address.
☒	☐	Information in the Orange Book has expired and the applicant needs to revise labeling.

Reviewer Comments:

Enter free text in this section as necessary.

Deficiency Comments:

- Standardized comments/deficiencies are available for certain questions. For a complete list of standardized comments, reference the [DLR Standardized Comments](#) SharePoint.
- Reviewers can modify standardized comments/deficiencies for their situation.
- Deficiencies will have a review number, deficiency number, and roman numeral in the user interface. For first original reviews the review number and iteration numeral will align; however, older reviews may have review numbers and iteration numerals that differ due to some reviews being completed under past practices.
- Deficiency comments will populate by default to the Labeling Comments deficiency section unless you select the Post-Approval checkbox. Assessors also have the option to move all comments to the Post-Approval Revisions section or vice versa from the Labeling Comments tab.

Deficiency Comments:

Creation Cycle	Category	Deficiency	Response/Recommendation	Post Approval
C7		Normal Text Standard		Post Approval

[Add Deficiency](#)

3 OVERALL ASSESSMENT OF MATERIALS REVIEWED (C7)

Table 1: Review Summary of Container Label and Carton Labeling

	Final or Draft or NA	Packaging Sizes	Submission Received Date	Recommendation
Container	Final	Bottles of 60s and 180s for 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg	10/30/2019	Satisfactory
Blister	N/A	N/A		
Carton	N/A	N/A		

Table 2: Review Summary of Prescribing Information and Patient Labeling

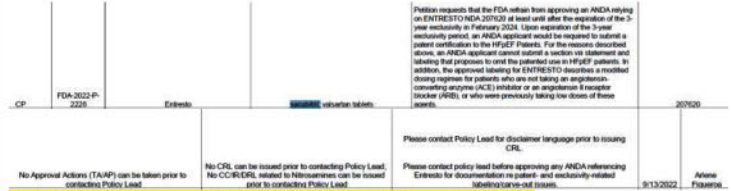
	Final or Draft or NA	Revision Date and/or Code	Submission Received Date	Recommendation
Prescribing Information	Final	Issued on: 07/2024	7/15/2024	Satisfactory
Medication Guide	N/A	N/A		
Patient Information	Final	Issued on: 04/2024	7/15/2024	Satisfactory
Instructions for Use	N/A	N/A		
SPL Data Elements				

4 LABELING REVIEW INFORMATION(C7)

4.1 REGULATORY INFORMATION (C7)

Yes	No	
☒	☐	Are there any applicable issues in DLR's SharePoint Drug Facts ? 1. (b)(4) Applicant includes pediatric information in the proposed labeling. 2. (b)(4) (b)(4)

Yes	No	
		(b)(4) We note that on September 12, 2022, Novartis Pharmaceuticals Corporation (Novartis) submitted a citizen petition (Docket No. FDA-2022-P-2228) requesting, among other things, that FDA refrain from approving any ANDA relying on NDA 207620 for Entresto as the reference listed drug until after the expiration of the following patents 1) U.S. Patent Nos. 9,517,226; 9,937,143; and 11,135,192, each expiring on August 22, 2033, and each listed in

Yes	No	
		the Orange Book with the patent use code “U-3084: (Treatment of Heart Failure With Preserved Ejection Fraction)” and (2) U.S. Patent No. 11,058,667 listed in the Orange Book, expiring May 9, 2036, and listed with the patent use code U-3170 (treating chronic heart failure with reduced ejection fraction in patients not taking an ace inhibitor or an ARB or previously taking low doses of these agents, by titrating up from half the usually recommended starting dose). The issues raised by that petition are under review by the agency and FDA has not made a final decision on the issues the petition raises. Nonetheless, in the interest of expediting processing of your ANDA in the event FDA concludes that applicants may carve out protected labeling, with this communication we are providing you with our current thinking about the labeling for your ANDA with the uses protected by patent s for which you have provided section viii statement s carved out of the label. These deficiency comments included in this communication/email reflect only our current thinking on ANDA labeling were FDA to determine that a labeling carve-out is possible, and this communication/email does not represent a final decision by the agency on the issues raised in the pending citizen petition. As such, additional changes to the proposed labeling of an ANDA for sacubitril and valsartan tablets may be required as the Agency continues to consider issues raised by this petition and Orange Book-listed patents.
☒	☐	Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? CP, FDA 2022-P-2228- HFpEF and Modified dosing P/E petition. checked PAL #20240624.  C6-Labeling will be impacted by the CP.

4.2 MODEL PRESCRIBING INFORMATION (C7)

Table 3: Review Model Labeling for Prescribing Information/Patient Labeling
(Check the box used as the Model Labeling)

☒ **MOST RECENTLY APPROVED NDA MODEL LABELING**

(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so, enter the most recently approved ANDA labeling information as applicable.)

NDA#/Supplement# (S-000 if original): NDA207620 / S-025

Supplement Approval Date: 04/12/2024

Proprietary Name: Entresto

Established Name: Sacubitril and Valsartan Tablets

Description of Supplement:

**Table 3: Review Model Labeling for Prescribing Information/Patient Labeling
(Check the box used as the Model Labeling)**

NDA 218591
NDA 207620/S-025

NDA APPROVAL

Novartis Pharmaceuticals Corporation
Attention: Byron Griffith, PhD
Senior Global Program Regulatory Manager
One Health Plaza
Building 337
East Hanover, New Jersey 07936-1080

Dear Dr. Griffith:

Please refer to your new drug application (NDA) and your supplemental new drug application (sNDA) dated June 14, 2023, received, June 14, 2023 and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for:

- Entresto Sprinkle (sacubitril/valsartan) oral pellets
- Entresto (sacubitril/valsartan) tablets

This NDA and sNDA provide for the use of Entresto (sacubitril/valsartan) tablets and oral pellets 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.

Link: <https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af8073a990>

☐ MOST RECENTLY APPROVED ANDA MODEL LABELING

☒ OTHER/TEMPLATE (e.g., Pending Supplements, BPCA, PREA, Carve-out):

•

•

(b)(4)

• OTHER IMPORTANT INFORMATION:

(b)(4)

- Supplements 14 to 15 (CMC supplements): N/A for labeling.

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	ANDA is up-to-date with the RLD/Model labeling.
Reviewer Comments:		
C6 Assessment on 6/28/2024:		
Proposed labeling		
(b)(4)		

- The Indications and Usage section was discussed internally and with feedback from OND, DLR
(b)(4)
- RLD/S-022, S-021, and (b)(4) are CMC only, pending supplements.

C7 Assessment on 7/16/2024: Proposed labeling aligns with RLD/S-025 (b)(4)

Deficiency Comments:

4.3 PATENTS AND EXCLUSIVITIES (C7)

The [Orange Book](#) was searched on 07/16/2024.

Table 4 provides Orange Book patents for the Model Labeling (NDA207620) and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 4: Impact of Model Labeling Patents on ANDA Labeling							
Strengths	Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	11058667	05/09/2036	U-3170	TREATING CHRONIC HEART FAILURE WITH REDUCED EJECTION FRACTION IN PATIENTS NOT TAKING AN ACE INHIBITOR OR AN ARB OR PREVIOUSLY TAKING LOW DOSES OF THESE AGENTS, BY TITRATING UP FROM HALF THE USUALLY RECOMMENDED STARTING DOSE	viii	12/22/2021	Carve-out
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	11135192	08/22/2033	U-3084	TREATMENT OF HEART FAILURE WITH PRESERVED EJECTION FRACTION	viii	12/22/2021	Carve-out
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	7468390*PED	05/27/2024			IV	03/23/2020	Expired

Table 4: Impact of Model Labeling Patents on ANDA Labeling

Strengths	Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	8101659	01/15/2025			IV	03/23/2020	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	8101659*PED	07/15/2025			IV	03/23/2020	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	8877938	05/27/2027			IV	03/23/2020	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	8877938*PED	11/27/2027			IV	03/23/2020	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	9388134	11/08/2026	U-1723	TREATMENT OF HEART FAILURE	IV	03/23/2020	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	9388134*PED	05/08/2027			IV	03/23/2020	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	9517226	08/22/2033	U-3084	TREATMENT OF HEART FAILURE WITH PRESERVED EJECTION FRACTION	viii	12/22/2021	Carve-out
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	9937143	08/22/2033	U-3084	TREATMENT OF HEART FAILURE WITH PRESERVED EJECTION FRACTION	viii	12/22/2021	Carve-out

Table 5 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 5: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling

Strengths	Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	M-82	02/16/2024	LABELING REVISIONS RELATED TO CLINICAL STUDIES	With respect to the exclusivity code M-82 expiring on February 16, 2024. The proposed labeling for the MSN product does not include information associated with the M-82 exclusivity.	12/22/2021	Carve-out

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	There is information in the Orange Book that the applicant needs to address.
☐	☒	Information in the Orange Book has expired and the applicant needs to revise labeling.

Reviewer Comments:**C6-Assessment: Inadequate**

- (b)(4)
- M-82 (while expired and remains in the OB) should remain carved out because M-82 Clinical Studies approved under S-018 (Paragon and Paramount) (b)(4). Applicant previously addressed M-82 with a carve out. In addition, S-025 (just approved) also updates section 8.5 (Geriatrics) with Paragon study information. Section 8.5 (Geriatric) should be revised as indicated below under section 5.4 in this review.

(b)(4)

Proposed labeling submitted 5/2/2024 is inadequate for minor carveout information. In addition, see updated (7.9.2024) CP disclaimer language under section 5.3 in this review.

C7 Assessment 7/16/2024:

Proposed labeling submitted 7/15/2024 carve-out of unexpired patents is adequate. The expired M-82 exclusivity remains carved out. Section 8.5 was revised as requested. For details, see Prescribing Information sections 5.3 and 5.4 below in this review.

Deficiency Comments:**4.4 UNITED STATES PHARMACOPEIA (USP) (C7)**

The [USP](#) was searched on 07/16/2024.

Table 6: USP

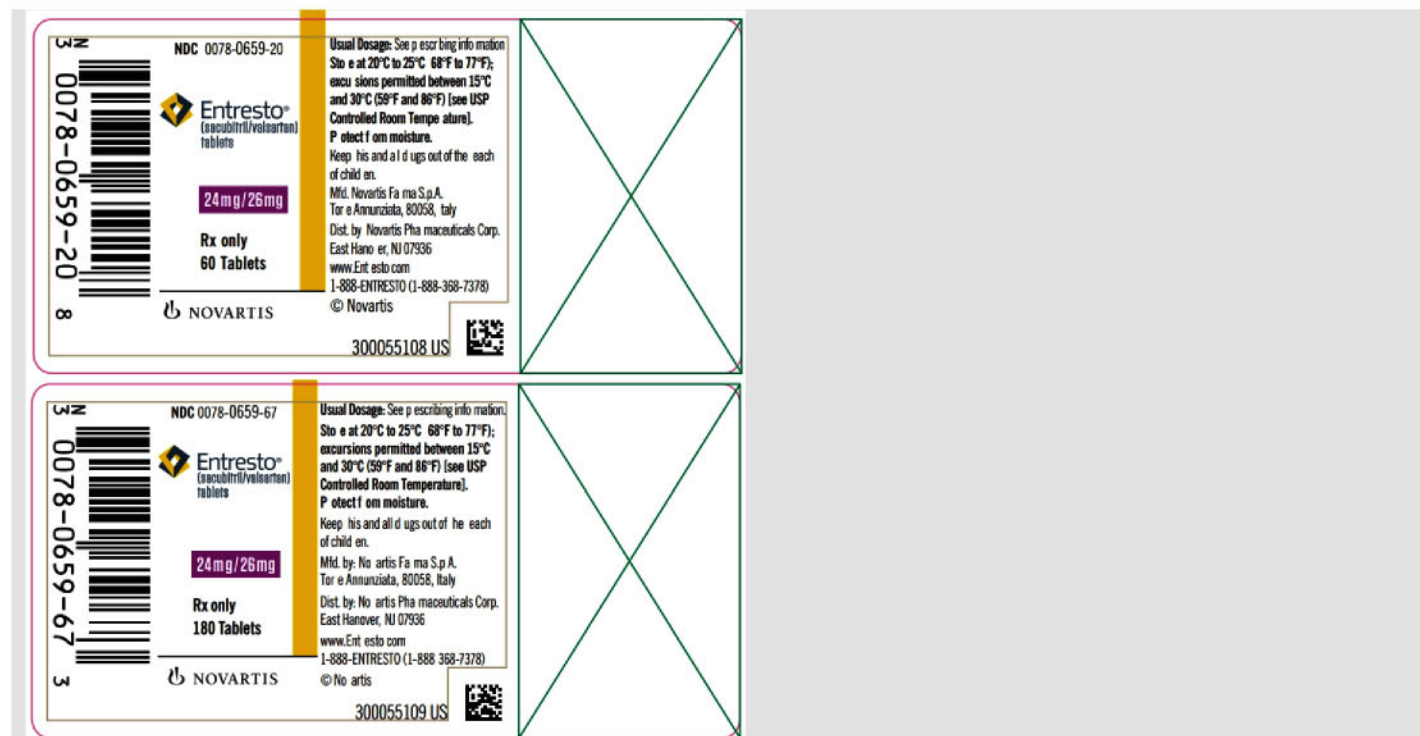
	YES or NO	Date	Monograph Title (N/A if no monograph)	Packaging and Storage/Labeling Statements (N/A if no monograph)
Currently Official	No		N/A	N/A
Not Yet Official	No		N/A	N/A

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Established name is acceptable with regard to the USP monograph or the RLD's nonproprietary name.
☐	☒	RLD's non-proprietary name is different from USP established name.
☐	☒	USP descriptor is correctly used in the appropriate sections of the prescribing information.
USP RECOMMENDATIONS and/or DIFFERENCES IN TEST METHODS (QUALITY):		
☐	☒	DISSOLUTION: The applicant's dissolution statement is appropriate.
☐	☒	ORGANIC IMPURITIES: Drug product meets USP acceptance criteria for organic impurities.
☐	☒	ASSAY: Drug product meets USP acceptance criteria for assay.
Reviewer Comments: None.		
Deficiency Comments:		

4.5 MODEL CONTAINER LABELS (C7)

Model container/carton/blister labels (Source: Drugs@FDA; SUPP-018 approved on 2/16/2021.)





5 ASSESSMENT OF ANDA LABELING AND LABELS (C7)

5.1 QUALITY INFORMATION (DRUG PRODUCT MOU & BIOPHARMACEUTICS) (C7)

5.1.1 DRUG PRODUCT REVIEW (C7)

Insert screenshot of Labeling portion from drug product review if completed:
Drug Product Review complete.

8/9/2023 DP Assessment: Adequate.

1.14 Labeling

Labeling & Prescribing Information

DESCRIPTION (Rx insert or Active Ingredient(s), and Inactive Ingredients in DRUG FACTS for OTC):

Is the information accurate? ☒ Yes ☐ No

If "No," explain.

Is the drug product subject of a USP monograph? ☐ Yes ☒ No

If "Yes," does labeling have accurate USP statement in the DESCRIPTION (for Rx) or Other Information section of DRUG FACTS (for OTC)?

☐ Yes ☐ No ☐ Statement not needed

If NO, what is/are the needed statement(s)? _____

HOW SUPPLIED section (Rx insert) or Storage (in DRUG FACTS for OTC)

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Is tamper evident feature provided in the container/closure for the OTC products or Controlled Substance (CII – CIV) products? ☐ Yes ☐ No
☒ N/A (NOT OTC or Controlled Substance)

If "No," explain.

For solid oral drug products, only: drug product length(s) of commercial batch(es):

ANDA Strength	Length (MM)	Imprint Code
24 mg/ 26 mg	10.00 x 4.00	one side debossed with 'M' and other side debossed with 'S1'
49 mg/ 51 mg	13.00 x 5.10	one side debossed with 'M' and other side debossed with 'S2'
97 mg/ 103 mg	15.00 x 5.90	one side debossed with 'M' and other side debossed with 'S3'

Send issue to the Labeling assessor through the Platform with a list of quality-related labeling deficiencies and also record reference number or link for all the issues:

Issue Description	Issue Reference Number or Link

LABELING LIST OF DEFICIENCIES

N/A

5.1.2 DESCRIPTION (C7)

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section

Model Labeling	ENTRESTO is available as film-coated tablets for oral administration, 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. The tablet inactive ingredients are colloidal silicon dioxide, crospovidone, low-substituted hydroxypropylcellulose, magnesium stearate (vegetable origin), microcrystalline cellulose, and talc. The film-coat inactive ingredients are hypromellose, iron oxide red (E172), polyethylene glycol 4000, talc, and titanium dioxide (E171). The film-coat for the 24 mg of sacubitril and 26 mg of valsartan tablet and the 97 mg of sacubitril and 103 mg of valsartan tablet also contains iron oxide black (E172). The film-coat for the 49 mg of sacubitril and 51 mg of valsartan tablet contains iron oxide yellow (E172). ENTRESTO SPRINKLE is available as film-coated oral pellets within capsules for oral administration, containing 8 mg of sacubitril and 6 mg of valsartan, and 15 mg of sacubitril and 16 mg of valsartan. The oral pellet inactive ingredients are colloidal silicon dioxide, hydroxypropylcellulose, magnesium stearate (vegetable origin), microcrystalline cellulose, and talc. The film-coat inactive ingredients are basic butylated methacrylate copolymer, sodium lauryl sulfate, stearic acid, and talc. The capsule shell inactive ingredients are hypromellose and titanium dioxide (E171). The capsule shell for the 15 mg of sacubitril and 16 mg of valsartan oral pellets also contains iron oxide yellow (E172). The printing ink contains shellac, propylene glycol, iron oxide red (E172), ammonia solution (concentrated), and potassium hydroxide. (b)(4)
Previous ANDA Labeling	C6: The tablet inactive ingredients are colloidal silicon dioxide, crospovidone, croscarmellose sodium, magnesium stearate, microcrystalline cellulose and talc. The film-coat inactive ingredients are hypromellose, titanium dioxide, macrogol, talc and iron oxide red. The film-coat for the 24 mg of sacubitril and 26 mg of valsartan tablet and 97 mg of sacubitril and 103 mg of valsartan tablet also contains iron oxide black. The film-coat for the 49 mg of sacubitril and 51 mg of valsartan tablet also contains iron oxide yellow. Reviewers Assessment: No changes noted from previous cycle.
Current ANDA Labeling	C7: The tablet inactive ingredients are colloidal silicon dioxide, crospovidone, croscarmellose sodium, magnesium stearate, microcrystalline cellulose and talc. The film-coat inactive ingredients are hypromellose, titanium dioxide, macrogol, talc and iron oxide red. The film-coat for the 24 mg of sacubitril and 26 mg of valsartan tablet and 97 mg of sacubitril and 103 mg of valsartan tablet also contains iron oxide black. The film-coat for the 49 mg of sacubitril and 51 mg of valsartan tablet also contains iron oxide yellow. Reviewers 7/16/2024 (C7) Assessment: No changes noted from previous cycle.

5.1.3 HOW SUPPLIED/STORAGE AND HANDLING (C7)

Table 8: Comparison of Model Labeling to ANDA Labeling

Model Labeling

16 HOW SUPPLIED/STORAGE AND HANDLING

ENTRESTO (sacubitril/valsartan) tablets are unscored, ovaloid, biconvex, and film-coated.

ENTRESTO film-coated oral pellets are round, biconvex in shape, and provided in a hard capsule.

All strengths are packaged in bottles as described below.

ENTRESTO Tablets				
Sacubitril/valsartan mg/mg	Color	Debossment Side 1/side 2	NDC 0078-XXXX-XX	
			Bottle of 60	Bottle of 180
24/26	Violet white	NVR/LZ	0659-20	0659-67
49/51	Pale yellow	NVR/L1	0777-20	0777-67
97/103	Light pink	NVR/L11	0696-20	0696-67

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Reference ID: 5363847

ENTRESTO SPRINKLE				
Sacubitril/valsartan mg/mg	Color	Print	NDC 0078-XXXX-XX	
			Bottle of 60	
6/6	White cap and transparent body	"NVR" and both parts with arrows and "04"	1231-20	
15/16	Yellow cap and transparent body	"NVR" and both parts with arrows and "10"	1238-20	

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.

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.

Assessor's note 7/16/2024: RLD is approved for pellets under a different NDA as a combined insert with tablets. This ANDA is not marketing that dosage form (pellets).

Previous ANDA Labeling

C6:
Sacubitril/valsartan tablets are available as unscored, oval shaped, 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. All strengths are packaged in bottles as described below.

Tablet	Color	Debossment	NDC # 69539-XXX-XX	
Sacubitril/Valsartan		"M" and	Bottle of 60	Bottle of 180
24 mg/26 mg	Purple	S1	166-60	166-18
49 mg/51 mg	Light yellow	S2	167-60	167-18
97 mg/103 mg	Light pink	S3	168-60	168-18

Store at 25°C (77°F), excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from moisture.

Reviewer's Assessment: No changes noted from previous cycle.

Current ANDA Labeling

Sacubitril/valsartan tablets are available as unscored, oval shaped, 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. All strengths are packaged in bottles as described below.

Table 8: Comparison of Model Labeling to ANDA Labeling

	Tablet	Color	Debossment	NDC # 69539-XXX-XX	
	Sacubitril/Valsartan		"M" and	Bottle of 60	Bottle of 180
	24 mg/26 mg	Purple	S1	166-60	166-18
	49 mg/51 mg	Light yellow	S2	167-60	167-18
	97 mg/103 mg	Light pink	S3	168-60	168-18
	Store at 25°C (77°F), excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from moisture. C7: Reviewer's Assessment 7/16/2024: No changes noted.				

5.1.4 MANUFACTURER, DISTRIBUTOR, AND/OR PACKER (C7)

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements

Previous ANDA Labeling	
Name and Address on ANDA Prescribing Information	Manufactured by: MSN Laboratories Private Limited Telangana – 509 228, INDIA Distributed by: MSN Pharmaceuticals Inc. Piscataway, NJ 08854 -3714 Issued on: 4/2024
Current ANDA Labeling	
Name and Address on ANDA Prescribing Information	Manufactured by: MSN Laboratories Private Limited Telangana – 509 228, INDIA Distributed by: MSN Pharmaceuticals Inc. Piscataway, NJ 08854 -3714 Issued on 7/2024

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements

Manufactured by	Manufactured for	Distributed by	Distributed for
-----------------	------------------	----------------	-----------------

5.2 CONTAINER LABEL (FOR BLISTERS GO TO UNIT-DOSE BLISTERS) (C7)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Container meets the too small exemption [21 CFR 201.10(i)]. Please enter Reviewer/Deficiency Comments if you select Deficiency.
ESTABLISHED/PROPRIETARY NAME and STRENGTH:		
☐	☒	Tall Man lettering complies with recommendations found on FDA webpage .
☐	☒	Established/proprietary name and strength are the most prominent information on the Principal Display Panel.
☐	☒	No intervening text (written, printed, or graphic matter) between established name and strength.
THE FOLLOWING COMPONENTS ARE PROPERLY DISPLAYED:		
☐	☒	Net quantity statement. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Dosage statement.
☐	☒	NDC number : prominence, linear bar code, and its orientation.
☐	☒	Expiration date and lot number (or placeholder).
☐	☒	Equivalency statement (product strength).
☐	☒	Medication Guide Pharmacist instructions [21 CFR 208.24(d)].
☐	☒	Controlled Substance Symbol .
☐	☒	Image of drug product represents the true size, color, and imprint.
☐	☒	Yellow #5 (tartrazine) warning statement is properly displayed.
☐	☒	Alcohol is properly listed [21 CFR 201.10(d)(2)].
☐	☒	Latex warning statement is properly displayed [21 CFR 801.437].
☐	☒	Gluten statement is appropriately stated.
PRODUCT DIFFERENTIATION:		
☐	☒	ANDA is the same color as the RLD labels as required (e.g. warfarin, levothyroxine, enoxaparin). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Multiple strengths are differentiated by use of different color or other acceptable means.
☐	☒	Labels of proposed product is differentiated from related products .
STORAGE, DISPENSING, MANUFACTURER, and PACKAGING:		
☐	☒	Storage/dispensing statement is consistent with the How Supplied section of the insert/RLD/USP. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Manufacturer/Distributor/Packager statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
☐	☒	Tamper evident (controlled substances) requirements are met.
☐	☒	Use of child-resistant closure (CRC) or non-CRC is appropriate. Describe container closure , cite source, and any issues in Reviewer Comments below.
OVERALL ASSESSMENT:		
☐	☒	Requirements met for the required label statements (21 CFR 201.15 and 21 CFR 201.100). Please enter Reviewer/Deficiency Comments if you select Deficiency.
Reviewer Comments: The 10/30/2019 container labels were determined adequate. Those labels will be attached to this review for completeness.		
Deficiency Comments:		

5.3 PRESCRIBING INFORMATION (C7)

Reviewer Assessment:

Deficiency	No Deficiency	
HIGHLIGHTS:		

Deficiency	No Deficiency	
☐	☒	Contact information for applicant and FDA are listed correctly.
☐	☒	Revision date appears at the end of HIGHLIGHTS section (PLR) or end of prescribing information (non-PLR).
DESCRIPTION/INACTIVE INGREDIENTS:		
Appropriate warning/precaution statements for inactive ingredients are present (21 CFR 201) Check only if applicable:		
☐	☒	☒ Sulfite (21 CFR 201.22) ☒ Yellow #5 (Tartrazine) (21 CFR 201.20) ☒ Phenylalanine/aspartame (21 CFR 201.21) ☒ Latex (21 CFR 801.437).
☐	☒	Sterile product statement [21 CFR 201.57(c)(12)(i)(D)].
☐	☒	Alcohol is properly listed [21 CFR 201.10(d)(2)].
☐	☒	Gluten statement is appropriately stated.
☐	☒	Dosage form, pharmacologic/therapeutic class, and route of administration properly listed [21 CFR 201.57(c)(12)(i)(B)] and [21 CFR 201.57(c)(12)(i)(E)].
HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:		
☐	☒	All submitted labels and labeling are consistent with the HOW SUPPLIED section.
☐	☒	Physical description (e.g. scoring, color, imprint, capsule size, nozzle tip, cap color) of the finished product in the HOW SUPPLIED section are appropriately displayed.
☐	☒	NDC numbers are present.
☐	☒	Drug product is the same color as the RLD's drug product as required (e.g. warfarin, levothyroxine, enoxaparin).
☐	☒	Storage or dispensing statement is acceptable compared to the RLD/USP monograph. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	"Discard unused portion" for single-dose products.
☐	☒	Manufacturer/Distributor/Packager statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
REGULATORY/OVERALL ASSESSMENT:		
☐	☒	STIC requirements addressed appropriately.
☐	☒	Intent to join the Antiretroviral Pregnancy Registry (APR) upon full approval.
☐	☒	Pregnancy registry information is appropriately included/excluded as required for the RLD.
☐	☒	Patent/exclusivity carve out is acceptable. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Dosage form/strength carve out (RLD combined labeling): justification for retaining information for safety/efficacy.
☐	☒	Prescribing information meets formatting requirements [21 CFR 201.57 (PLR) or 21 CFR 201.80 (non-PLR)].
☐	☒	Prescribing Information is the same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8). Please enter Reviewer/Deficiency Comments if you select Deficiency.
Reviewer Comments: C6- 6/28/2024 Assessment: Inadequate • (b)(4) • (b)(4) (b)(4) (b)(4) (b)(4)		

Proposed Prescribing information submitted 5/2/2024 is inadequate. Additionally, the 7.9.2024 Policy CP disclaimer language will be issued for inadequate assessment.

Note:

(b)(4)

C7 Assessment on 7/16/2024: Adequate

-
-
- Prescribing Information and Patient Leaflet submitted on 7/15/2024 are adequate.

Deficiency Comments:

Deficiency # 1

HIGHLIGHTS, DOSAGE AND ADMINISTRATION, 3rd bullet in RLD labeling,

Created in C6

Prescribing Information

(b)(4)

Response / Assessment:

Addressed adequately in the 7/15/2024 submission.

Deficiency # 2

INDICATIONS AND USAGE, Section 1.1 Adult Heart Failure, 2nd paragraph revise to read as follows:

Created in C6

Prescribing Information

"Left ventricular ejection fraction (LVEF) is a variable measure..." [Note-include the wording for the acronym "LVEF".]

Response / Assessment:

Adequately addressed in the 7/15/2024 submission.

Deficiency # 3

Geriatric Use, Section 8.5. Revise first paragraph to read as follows

(b)(4)

Created in C6

Prescribing Information

Geriatric Use

"There were 4,143 heart failure patients 65 years of age and older in PARADIGM-HF [see Clinical Studies (14)]. Of the total number of sacubitril and valsartan-treated patients, 2,087 (49.6%) were 65 years of age and older, while 786 (18.7%) were 75 years of age and older in PARADIGM-HF. No overall differences in safety or effectiveness of sacubitril and valsartan have been observed between patients 65 years of age and older and younger adult patients."

No relevant pharmacokinetic differences...

Response / Assessment:

Adequately addressed in the 7/15/2024 submission.

Deficiency # 4

We note that on September 12, 2022, Novartis Pharmaceuticals Corporation (Novartis) submitted a citizen petition (Docket No. FDA-

Created in C6

General Comments

2022-P-2228) requesting, among other things, that FDA refrain from approving any ANDA relying on NDA 207620 for Entresto as the reference listed drug until after the expiration of the following patents 1) U.S. Patent Nos. 9,517,226; 9,937,143; and 11,135,192, each expiring on August 22, 2033, and each listed in the Orange Book with the patent use code “U-3084: (Treatment of Heart Failure With Preserved Ejection Fraction)” and (2) U.S. Patent No. 11,058,667 listed in the Orange Book, expiring May 9, 2036, and listed with the patent use code U-3170 (treating chronic heart failure with reduced ejection fraction in patients not taking an ace inhibitor or an ARB or previously taking low doses of these agents, by titrating up from half the usually recommended starting dose). The issues raised by that petition are under review by the agency and FDA has not made a final decision on the issues the petition raises. Nonetheless, in the interest of expediting processing of your ANDA in the event FDA concludes that applicants may carve out protected labeling, with this communication we are providing you with our current thinking about the labeling for your ANDA with the uses protected by patents for which you have provided section viii statements carved out of the label. These deficiency comments included in this communication/email reflect only our current thinking on ANDA labeling were FDA to determine that a labeling carve-out is possible, and this communication/email does not represent a final decision by the agency on the issues raised in the pending citizen petition. As such, additional changes to the proposed labeling of an ANDA for sacubitril and valsartan tablets may be required as the Agency continues to consider issues raised by this petition and Orange Book-listed patents.

Response / Assessment:

Acknowledged in the 7/15/2024 submission.

5.4 OTHER PATIENT LABELING (C7)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Other patient labeling is the same as the model labeling except for allowable differences. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

C6- 6/28/2024: Adequate

(b)(4)

C7, 7/16/2024: Adequate

-
- Patient leaflet resubmitted on 7/15/2024 is adequate.

Deficiency Comments:

6 COMMENTS/CONSULTS FOR OTHER DISCIPLINES (C7)

A labeling statement required verification from another division discipline. Check only if applicable.

Reviewer Assessment:

☐	Rubber
☐	Latex
☐	Gluten
☐	Alcohol (ethanol)
☐	Aluminum (small/large volume parenteral and pharmacy bulk package)
☐	Sulfite
☐	Phenylalanine (aspartame) - content calculation
☐	Yellow #5 (tartrazine)
☐	Ghost tablet/capsule (i.e. solid or semi-solid mass in stool)
☐	Other

Describe questions/issue(s) sent to and/or received from other discipline(s) (e.g., OPQ, OB): (For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue)

Reviewer Comments:

For The Record-from previous cycles.

(b)(4)

Deficiency Comments:



Angela
Payne

Digitally signed by Angela Payne
Date: 7/17/2024 08:38:18AM
GUID: 508da70600028ab611d2ba935d5074a6



Burhan
Nour

Digitally signed by Burhan Nour
Date: 7/17/2024 01:32:34PM
GUID: 508da70600028ae6e75df33aa0f5b2ce

Labeling Review

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	June 28, 2024, and July 9, 2024
ANDA Number(s)	213748
Review Number	6
Applicant Name	MSN Laboratories Private Limited
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Sacubitril and Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg
Proposed Proprietary Name	None
Submission Received Date	May 2, 2024
Primary Labeling Reviewer	Angela Payne, RPh
Secondary Labeling Reviewer	Refer to signature page
Review Conclusion ☐ Acceptable - No Comments ☐ Acceptable - Include Post Approval Comments ☒ Minor Deficiency* - Refer to Labeling Deficiencies and Comments for Letter to Applicant ☐ Major Deficiency** - Refer to Labeling Deficiencies and Comments for Letter to Applicant *Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.	
On Policy Alert List	☒ Yes ☐ No
Acceptable For Filing	☒ Yes ☐ No
Combined Insert/Outsert	☐ Yes ☒ No

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1 **LABELING COMMENTS (C6)**

1.1 **LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT (C6)**

The following comments have been identified by the Division of Labeling Review (DLR) based on your submission(s) on May 2, 2024.

Prior to final approval, the proposed labeling should be clear and precise (grammar, spelling, and formatting) for end users, and accurately reflect the Reference Listed Drug (RLD) information to comply with FDA policies, laws, regulations (i.e., 21 CFR 314.94(a)(8)), official compendia, and relevant guidance.

1. GENERAL COMMENT

We note that on September 12, 2022, Novartis Pharmaceuticals Corporation (Novartis) submitted a citizen petition (Docket No. FDA-2022-P-2228) requesting, among other things, that FDA refrain from approving any ANDA relying on NDA 207620 for Entresto as the reference listed drug until after the expiration of the following patents 1) U.S. Patent Nos. 9,517,226; 9,937,143; and 11,135,192, each expiring on August 22, 2033, and each listed in the Orange Book with the patent use code "U-3084: (Treatment of Heart Failure With Preserved Ejection Fraction)" and (2) U.S. Patent No. 11,058,667 listed in the Orange Book, expiring May 9, 2036, and listed with the patent use code U-3170 (treating chronic heart failure with reduced ejection fraction in patients not taking an ace inhibitor or an ARB or previously taking low doses of these agents, by titrating up from half the usually recommended starting dose). The issues raised by that petition are under review by the agency and FDA has not made a final decision on the issues the petition raises. Nonetheless, in the interest of expediting processing of your ANDA in the event FDA concludes that applicants may carve out protected labeling, with this communication we are providing you with our current thinking about the labeling for your ANDA with the uses protected by patents for which you have provided section viii statements carved out of the label. These deficiency comments included in this communication/email reflect only our current thinking on ANDA labeling were FDA to determine that a labeling carve-out is possible, and this communication/email does not represent a final decision by the agency on the issues raised in the pending citizen petition. As such, additional changes to the proposed labeling of an ANDA for sacubitril and valsartan tablets may be required as the Agency continues to consider issues raised by this petition and Orange Book-listed patents.

2. PRESCRIBING INFORMATION

- a. HIGHLIGHTS, DOSAGE AND ADMINISTRATION, 3rd bullet in RLD labeling,

(b)(4)

- b. INDICATIONS AND USAGE, Section 1.1 Adult Heart Failure, 2nd paragraph revise to read as follows:

"Left ventricular ejection fraction (LVEF) is a variable measure..." [Note- include the wording for the acronym "LVEF".]

- c. Geriatric Use, Section 8.5, Revise first paragraph to read as follows

(b)(4)

(b)(4)

Geriatric Use

"There were 4,143 heart failure patients 65 years of age and older in PARADIGM-HF [see Clinical Studies (14)]. Of the total number of sacubitril and valsartan-treated patients, 2,087 (49.6%) were 65 years of age and older, while 786 (18.7%) were 75 years of age and older in PARADIGM-HF. No overall differences in safety or effectiveness of sacubitril and valsartan have been observed between patients 65 years of age and older and younger adult patients."

No relevant pharmacokinetic differences...

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book (OB), and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE (C6)

1.3 POST-APPROVAL REVISIONS (C6)

These comments will be addressed post approval (in the first labeling supplement review).

2 INSTRUCTIONS FOR ASSESSMENT (C6)

General Comments:

Select the "no deficiency" or "deficiency" radio button as appropriate for each row. If a "Deficiency Comments" appears, ensure it is appropriate for your situation, edit, or enter "Reviewer Comments" if necessary.

If there is no issue/concern, or if the question is not applicable. No "Deficiency Comments" will appear but reviewers can still enter "Reviewer Comments" if desired.

☐	☒	There is information in the Orange Book that the applicant needs to address.
☒	☐	Information in the Orange Book has expired and the applicant needs to revise labeling.

Reviewer Comments:

Enter free text in this section as necessary.

Deficiency Comments:

- Standardized comments/deficiencies are available for certain questions. For a complete list of standardized comments, reference the [DLR Standardized Comments](#) SharePoint.
- Reviewers can modify standardized comments/deficiencies for their situation.
- Deficiencies will have a review number, deficiency number, and roman numeral in the user interface. For first original reviews the review number and iteration numeral will align; however, older reviews may have review numbers and iteration numerals that differ due to some reviews being completed under past practices.
- Deficiency comments will populate by default to the Labeling Comments deficiency section unless you select the Post-Approval checkbox. Assessors also have the option to move all comments to the Post-Approval Revisions section or vice versa from the Labeling Comments tab.

The screenshot shows a web interface for 'Deficiency Comments'. It features a table with the following columns: 'Creation Cycle', 'Category', 'Deficiency', 'Response/Assessment', and 'Post-Approval'. The 'Post-Approval' column contains a checkbox. A red arrow points from the 'Deficiency' column to this checkbox, indicating a function to move comments to the Post-Approval section. Below the table, there is an 'Add Deficiency' link.

3 OVERALL ASSESSMENT OF MATERIALS REVIEWED (C6)

Table 1: Review Summary of Container Label and Carton Labeling

	Final or Draft or NA	Packaging Sizes	Submission Received Date	Recommendation
Container	Final	Bottles of 60s and 180s for 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg	10/30/2019	Satisfactory
Blister	N/A	N/A		
Carton	N/A	N/A		

Table 2: Review Summary of Prescribing Information and Patient Labeling

	Final or Draft or NA	Revision Date and/or Code	Submission Received Date	Recommendation
Prescribing Information	Draft	Issued on: 4/2024	5/2/2024	Revise
Medication Guide	N/A	N/A		
Patient Information	Draft	Issued on: 4/2024	5/2/2024	Satisfactory
Instructions for Use	N/A	N/A		
SPL Data Elements				

4 LABELING REVIEW INFORMATION(C6)

4.1 REGULATORY INFORMATION (C6)

Yes	No	
☒	☐	Are there any applicable issues in DLR's SharePoint Drug Facts? 1. Applicant includes pediatric information in the proposed labeling. 2. (b)(4) (b)(4) (b)(4)

Yes	No	
		REVISED ENTRESTO CP DISCLAIMER LANGUAGE (to include ____ language, so we can communicate the current thinking on the carveout to applicants after OCC clearance) We note that on September 12, 2022, Novartis Pharmaceuticals Corporation (Novartis) submitted a citizen petition (Docket No. FDA-2022-P-2228) requesting, among other things, that FDA refrain from approving any ANDA relying on NDA 207620 for Entresto as the reference listed drug until after the expiration of the following patents 1) U.S. Patent Nos. 9,517,226; 9,937,143; and 11,135,192, each expiring on August 22, 2033, and each listed in the Orange Book with the patent use code “U-3084: (Treatment of Heart Failure With Preserved Ejection Fraction)” and (2) U.S. Patent No. 11,058,667 listed in the Orange Book, expiring May 9, 2036, and listed with the patent use code U-3170 (treating chronic heart failure with reduced ejection fraction in patients not taking an ace inhibitor or an ARB or previously taking low doses of these agents, by titrating up from half the usually recommended starting dose). The issues raised by that petition are under review by the agency and FDA has not made a final decision on the issues the petition raises. Nonetheless, in the interest of expediting processing of your ANDA in the event FDA concludes that applicants may carve out protected labeling, with this communication we are providing you with our current thinking about the labeling for your ANDA with the uses protected by patent s for which you have provided section viii statement s carved out of the label. These deficiency comments included in this communication/email reflect only our current thinking on ANDA labeling were FDA to determine that a labeling carve-out is possible, and this communication/email does not represent a final decision by the agency on the issues raised in the pending citizen petition. As such, additional changes to the proposed labeling of an ANDA for sacubitril and valsartan tablets may be required as the Agency continues to consider issues raised by this petition and Orange Book-listed patents.
☒	☐	Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? CP, FDA 2022-P-2228- HFpEF and Modified dosing P/E petition. checked PAL #20240624.

4.2 MODEL PRESCRIBING INFORMATION (C6)

Table 3: Review Model Labeling for Prescribing Information/Patient Labeling
(Check the box used as the Model Labeling)

☒ MOST RECENTLY APPROVED NDA MODEL LABELING

(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so, enter the most recently approved ANDA labeling information as applicable.)

NDA#/Supplement# (S-000 if original): NDA207620 / S-025

Supplement Approval Date: 04/12/2024

Proprietary Name: Entresto

Table 3: Review Model Labeling for Prescribing Information/Patient Labeling
(Check the box used as the Model Labeling)

Established Name: Sacubitril and Valsartan Tablets

Description of Supplement:

NDA 218591
NDA 207620/S-025

NDA APPROVAL

Novartis Pharmaceuticals Corporation
Attention: Byron Griffith, PhD
Senior Global Program Regulatory Manager
One Health Plaza
Building 337
East Hanover, New Jersey 07936-1080

Dear Dr. Griffith:

Please refer to your new drug application (NDA) and your supplemental new drug application (sNDA) dated June 14, 2023, received, June 14, 2023 and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for:

- Entresto Sprinkle (sacubitril/valsartan) oral pellets
- Entresto (sacubitril/valsartan) tablets

This NDA and sNDA provide for the use of Entresto (sacubitril/valsartan) tablets and oral pellets 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.

Link: <https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af8073a990>

☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING**

☒ **OTHER/TEMPLATE (e.g., Pending Supplements, BPCA, PREA, Carve-out):**

(b)(4)

3. OTHER IMPORTANT INFORMATION:

(b)(4)

- Supplements 14 to 15 (CMC supplements): N/A for labeling.

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	ANDA is up-to-date with the RLD/Model labeling.
Reviewer Comments:		
C6 Assessment on 6/28/2024:		
Proposed labeling	(b)(4)	
(b)(4)		

- The Indications and Usage section was discussed internally and with feedback from OND, DLR has

(b)(4)

- RLD/S-022, S-021, and [REDACTED] are CMC only, pending supplements.

Deficiency Comments:

4.3 PATENTS AND EXCLUSIVITIES (C6)

The [Orange Book](#) was searched on 06/28/2024.

Table 4 provides Orange Book patents for the Model Labeling (NDA207620) and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 4: Impact of Model Labeling Patents on ANDA Labeling							
Strengths	Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	11058667	05/09/2036	U-3170	TREATING CHRONIC HEART FAILURE WITH REDUCED EJECTION FRACTION IN PATIENTS NOT TAKING AN ACE INHIBITOR OR AN ARB OR PREVIOUSLY TAKING LOW DOSES OF THESE AGENTS, BY TITRATING UP FROM HALF THE USUALLY RECOMMENDED STARTING DOSE	viii	12/22/2021	Carve-out
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	11135192	08/22/2033	U-3084	TREATMENT OF HEART FAILURE WITH PRESERVED EJECTION FRACTION	viii	12/22/2021	Carve-out
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	7468390*PED	05/27/2024			IV	03/23/2020	Expired
24 mg;26 mg, 49 mg;51 mg,	8101659	01/15/2025			IV	03/23/2020	None

Table 4: Impact of Model Labeling Patents on ANDA Labeling							
Strengths	Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
97 mg;103 mg							
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	8101659*PED	07/15/2025			IV	03/23/2020	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	8877938	05/27/2027			IV	03/23/2020	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	8877938*PED	11/27/2027			IV	03/23/2020	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	9388134	11/08/2026	U-1723	TREATMENT OF HEART FAILURE	IV	03/23/2020	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	9388134*PED	05/08/2027			IV	03/23/2020	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	9517226	08/22/2033	U-3084	TREATMENT OF HEART FAILURE WITH PRESERVED EJECTION FRACTION	viii	12/22/2021	Carve-out
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	9937143	08/22/2033	U-3084	TREATMENT OF HEART FAILURE WITH PRESERVED EJECTION FRACTION	viii	12/22/2021	Carve-out

Table 5 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 5: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling

Strengths	Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	M-82	02/16/2024	LABELING REVISIONS RELATED TO CLINICAL STUDIES	With respect to the exclusivity code M-82 expiring on February 16, 2024. The proposed labeling for the MSN product does not include information associated with the M-82 exclusivity.	12/22/2021	Carve-out

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	There is information in the Orange Book that the applicant needs to address.
☐	☒	Information in the Orange Book has expired and the applicant needs to revise labeling.

Reviewer Comments:

C6-Assessment on 6/28/2024:

- (b)(4)
- M-82 (while expired and remains in the OB) should remain carved out because M-82 Clinical Studies approved under S-018 (Paragon and Paramount) (b)(4) Applicant previously addressed M-82 with a carve out. In addition, S-025 (just approved) also updates section 8.5 (Geriatrics) with Paragon study information. Section 8.5 (Geriatric) should be revised as indicated below under section 5.4 in this review.

(b)(4)

Proposed labeling submitted 5/2/2024 is inadequate for minor carveout information. In addition, See updated 7.9.2024 CP disclaimer language under section 5.4 in this review.

Deficiency Comments:

Deficiency # 1

Created in C5

General Comments

(b)(4)

Response / Assessment:

a.

b.

(b)(4)

Deficiency # 2	We note that on September 12, 2022, Novartis Pharmaceuticals Corporation (Novartis) submitted a citizen petition (Docket No. FDA-2022-P-2228) requesting, among other things, that FDA refrain from approving any ANDA relying on NDA 207620 for Entresto as the reference listed drug until after the expiration of the following patents 1) U.S. Patent Nos. 9,517,226; 9,937,143; and 11,135,192, each expiring on August 22, 2033, and each listed in the Orange Book with the patent use code “U-3084: (Treatment of Heart Failure With Preserved Ejection Fraction)” and (2) U.S. Patent No. 11,058,667 listed in the Orange Book, expiring May 9, 2036, and listed with the patent use code U-3170 (treating chronic heart failure with reduced ejection fraction in patients not taking an ace inhibitor or an ARB or previously taking low doses of these agents, by titrating up from half the usually recommended starting dose). In this complete response letter, we have included only comments that are unrelated to the citizen petition issues (FDA-2022-P-2228). Per Section XI, paragraph E of the GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2023-2027 (“GDUFA III Commitment Letter”), a response that addresses all other issues unrelated to the citizen petition is still considered a complete response. Since the citizen petition raises labeling issues that would delay only part of a complete response, we are including only comments unrelated to the pending citizen petition until a citizen response has been finalized. Additional changes to the proposed labeling of an ANDA for sacubitril and valsartan tablets may be required as the Agency continues to consider issues raised by this petition and Orange Book-listed patents. We also note that on April 18, 2019, Novartis submitted a citizen petition to FDA (Docket No. FDA-2019-P-1893) requesting that FDA require ANDAs that reference ENTRESTO (sacubitril and valsartan) tablets to demonstrate active pharmaceutical ingredient (API) sameness based on the chemical structure of the sacubitril and valsartan active ingredients present in the finished dosage form; revise FDA’s draft product-specific guidance (PSG) on sacubitril and valsartan oral tablets to recommend API sameness be established by showing that the chemical structure of each API in the finished dosage form of a proposed generic is identical to the chemical structure of each API in the RLD; and further revise the PSG to include other criteria. The issues raised by these citizen petitions are currently under review by the Agency, and FDA has not made a final decision on the issues the petitions raise. The comments included in this communication reflect only our current thinking, and this communication does not represent a final decision by the Agency on the issues raised in the pending citizen petitions.
Created in C5	
General Comments	
Response / Assessment:	Adequate in the 5/2/2024 submission. See updated 7.9.2024 CP disclaimer language under section 5.4 in this review.

4.4 UNITED STATES PHARMACOPEIA (USP) (C6)

The [USP](#) was searched on 07/01/2024.

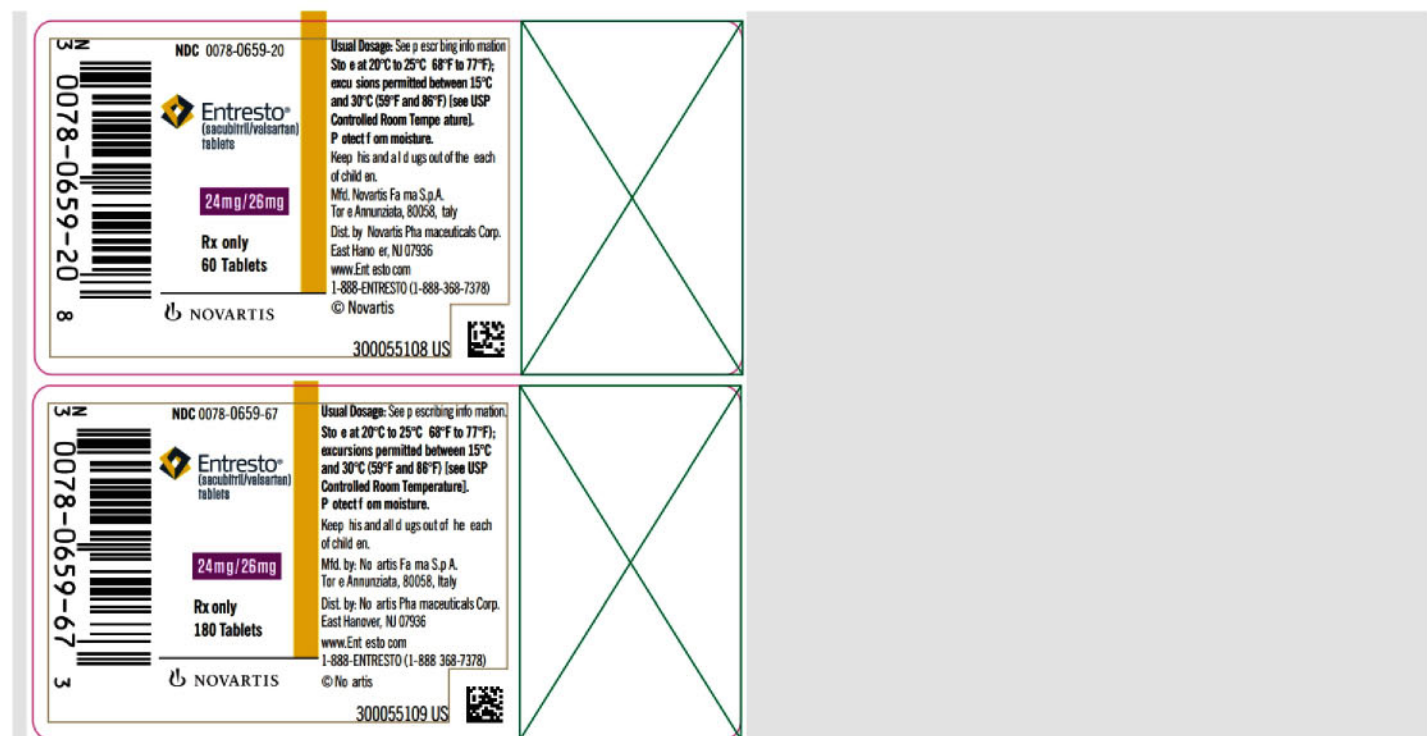
Table 6: USP				
	YES or NO	Date	Monograph Title (N/A if no monograph)	Packaging and Storage/Labeling Statements (N/A if no monograph)
Currently Official	No		N/A	N/A
Not Yet Official	No		N/A	N/A

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Established name is acceptable with regard to the USP monograph or the RLD's nonproprietary name.
☐	☒	RLD's non-proprietary name is different from USP established name.
☐	☒	USP descriptor is correctly used in the appropriate sections of the prescribing information.
USP RECOMMENDATIONS and/or DIFFERENCES IN TEST METHODS (QUALITY):		
☐	☒	DISSOLUTION: The applicant's dissolution statement is appropriate.
☐	☒	ORGANIC IMPURITIES: Drug product meets USP acceptance criteria for organic impurities.
☐	☒	ASSAY: Drug product meets USP acceptance criteria for assay.
Reviewer Comments: None		
Deficiency Comments:		

4.5 MODEL CONTAINER LABELS (C6)

Model container/carton/blister labels (Source: Drugs@FDA; SUPP-018 approved on 2/16/2021)





5 ASSESSMENT OF ANDA LABELING AND LABELS (C6)

5.1 QUALITY INFORMATION (DRUG PRODUCT MOU & BIOPHARMACEUTICS) (C6)

5.1.1 DRUG PRODUCT REVIEW (C6)

Insert screenshot of Labeling portion from drug product review if completed:
Drug Product Review complete.

8/9/2023 DP Assessment: Adequate

1.14 Labeling

Labeling & Prescribing Information

DESCRIPTION (Rx insert or Active Ingredient(s), and Inactive Ingredients in DRUG FACTS for OTC):

Is the information accurate? ☒ Yes ☐ No

If "No," explain.

Is the drug product subject of a USP monograph? ☐ Yes ☒ No

If "Yes," does labeling have accurate USP statement in the DESCRIPTION (for Rx) or Other Information section of DRUG FACTS (for OTC)?

☐ Yes ☐ No ☐ Statement not needed

If NO, what is/are the needed statement(s)? _____

HOW SUPPLIED section (Rx insert) or Storage (in DRUG FACTS for OTC)

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Is tamper evident feature provided in the container/closure for the OTC products or Controlled Substance (CII – CIV) products? ☐ Yes ☐ No
☒ N/A (NOT OTC or Controlled Substance)

If "No," explain.

For solid oral drug products, only: drug product length(s) of commercial batch(es):

ANDA Strength	Length (MM)	Imprint Code
24 mg/ 26 mg	10.00 x 4.00	one side debossed with 'M' and other side debossed with 'S1'
49 mg/ 51 mg	13.00 x 5.10	one side debossed with 'M' and other side debossed with 'S2'
97 mg/ 103 mg	15.00 x 5.90	one side debossed with 'M' and other side debossed with 'S3'

Send issue to the Labeling assessor through the Platform with a list of quality-related labeling deficiencies and also record reference number or link for all the issues:

Issue Description	Issue Reference Number or Link

LABELING LIST OF DEFICIENCIES

N/A

5.1.2 DESCRIPTION (C6)

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Model Labeling	The tablet inactive ingredients are microcrystalline cellulose, low-substituted hydroxypropylcellulose, crospovidone, magnesium stearate (vegetable origin), talc, and colloidal silicon dioxide. The film-coat inactive ingredients are hypromellose, titanium dioxide (E 171), Macrogol 4000, talc, and iron oxide red (E 172). The film-coat for the 24 mg of sacubitril and 26 mg of valsartan tablet and the 97 mg of sacubitril and 103 mg of valsartan tablet also contains iron oxide black (E 172). The film-coat for the 49 mg of sacubitril and 51 mg of valsartan tablet contains iron oxide yellow (E 172). <i>(Assessor's 7/9/2024 note: RLD S/025 is combined with pellets (new dosage form) not being offered and omitted by the ANDA sponsor).</i>
Previous ANDA Labeling	C5: The tablet inactive ingredients are colloidal silicon dioxide, crospovidone, croscarmellose sodium, magnesium stearate, microcrystalline cellulose and talc. The film-coat inactive ingredients are hypromellose, titanium dioxide, macrogol, talc and iron oxide red. The film-coat for the 24 mg of sacubitril and 26 mg of valsartan tablet and 97 mg of sacubitril and 103 mg of valsartan tablet also contains iron oxide black. The film-coat for the 49 mg of sacubitril and 51 mg of valsartan tablet also contains iron oxide yellow.
Current ANDA Labeling	C6: The tablet inactive ingredients are colloidal silicon dioxide, crospovidone, croscarmellose sodium, magnesium stearate, microcrystalline cellulose and talc. The film-coat inactive ingredients are hypromellose, titanium dioxide, macrogol, talc and iron oxide red. The film-coat for the 24 mg of sacubitril and 26 mg of valsartan tablet and 97 mg of sacubitril and 103 mg of valsartan tablet also contains iron oxide black. The film-coat for the 49 mg of sacubitril and 51 mg of valsartan tablet also contains iron oxide yellow. Reviewers Assessment: No changes noted.

5.1.3 HOW SUPPLIED/STORAGE AND HANDLING (C6)

Table 8: Comparison of Model Labeling to ANDA Labeling				
Model Labeling	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. All strengths are packaged in bottles as described below.			
	Tablet	Color	Debossment	NDC # 0078-XXXX-XX
	Sacubitril/Valsartan		“NVR” and	Bottle of 60 Bottle of 180
	24 mg/26 mg	Violet white	LZ	0659-20 0659-67
	49 mg/51 mg	Pale yellow	L1	0777-20 0777-67
	97 mg/103 mg	Light pink	L11	0696-20 0696-67

Table 8: Comparison of Model Labeling to ANDA Labeling

	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.																									
Previous ANDA Labeling	C5: Sacubitril/valsartan tablets are available as unscored, oval shaped, 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. All strengths are packaged in bottles as described below. <table><tr><th>Tablet</th><th>Color</th><th>Debossment</th><th colspan="2">NDC # 69539-XXX-XX</th></tr><tr><td>Sacubitril/Valsartan</td><td></td><td>"M" and</td><td>Bottle of 60</td><td>Bottle of 180</td></tr><tr><td>24 mg/26 mg</td><td>Purple</td><td>S1</td><td>166-60</td><td>166-18</td></tr><tr><td>49 mg/51 mg</td><td>Light yellow</td><td>S2</td><td>167-60</td><td>167-18</td></tr><tr><td>97 mg/103 mg</td><td>Light pink</td><td>S3</td><td>168-60</td><td>168-18</td></tr></table> Store at 25°C (77°F), excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from moisture. Reviewers Assessment from C5: Acceptable: No changes noted. We do note that the RLD has a slightly different storage temperature (b)(4) the DP assessor found this adequate. Refer to the HOW SUPPLIED section of their review in section 5.1.1 above.	Tablet	Color	Debossment	NDC # 69539-XXX-XX		Sacubitril/Valsartan		"M" and	Bottle of 60	Bottle of 180	24 mg/26 mg	Purple	S1	166-60	166-18	49 mg/51 mg	Light yellow	S2	167-60	167-18	97 mg/103 mg	Light pink	S3	168-60	168-18
Tablet	Color	Debossment	NDC # 69539-XXX-XX																							
Sacubitril/Valsartan		"M" and	Bottle of 60	Bottle of 180																						
24 mg/26 mg	Purple	S1	166-60	166-18																						
49 mg/51 mg	Light yellow	S2	167-60	167-18																						
97 mg/103 mg	Light pink	S3	168-60	168-18																						
Current ANDA Labeling	C6: Sacubitril/valsartan tablets are available as unscored, oval shaped, 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. All strengths are packaged in bottles as described below. <table><tr><th>Tablet</th><th>Color</th><th>Debossment</th><th colspan="2">NDC # 69539-XXX-XX</th></tr><tr><td>Sacubitril/Valsartan</td><td></td><td>"M" and</td><td>Bottle of 60</td><td>Bottle of 180</td></tr><tr><td>24 mg/26 mg</td><td>Purple</td><td>S1</td><td>166-60</td><td>166-18</td></tr><tr><td>49 mg/51 mg</td><td>Light yellow</td><td>S2</td><td>167-60</td><td>167-18</td></tr><tr><td>97 mg/103 mg</td><td>Light pink</td><td>S3</td><td>168-60</td><td>168-18</td></tr></table> Store at 25°C (77°F), excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from moisture. Reviewer's Assessment: No changes noted.	Tablet	Color	Debossment	NDC # 69539-XXX-XX		Sacubitril/Valsartan		"M" and	Bottle of 60	Bottle of 180	24 mg/26 mg	Purple	S1	166-60	166-18	49 mg/51 mg	Light yellow	S2	167-60	167-18	97 mg/103 mg	Light pink	S3	168-60	168-18
Tablet	Color	Debossment	NDC # 69539-XXX-XX																							
Sacubitril/Valsartan		"M" and	Bottle of 60	Bottle of 180																						
24 mg/26 mg	Purple	S1	166-60	166-18																						
49 mg/51 mg	Light yellow	S2	167-60	167-18																						
97 mg/103 mg	Light pink	S3	168-60	168-18																						

5.1.4 MANUFACTURER, DISTRIBUTOR, AND/OR PACKER (C6)

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements

Previous ANDA Labeling	
Name and Address on ANDA Prescribing Information	Manufactured by: MSN Laboratories Private Limited Telangana – 509 228, INDIA Distributed by: MSN Pharmaceuticals Inc. Piscataway, NJ 08854 -3714 Issued on: 12/2022
Current ANDA Labeling	
Name and Address on ANDA Prescribing Information	Manufactured by: MSN Laboratories Private Limited Telangana – 509 228, INDIA Distributed by: MSN Pharmaceuticals Inc. Piscataway, NJ 08854 -3714 Issued on 4/2024 Reviewers Assessment: No changes noted except for updated revision date.

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements

Manufactured by	Manufactured for	Distributed by	Distributed for
-----------------	------------------	----------------	-----------------

5.2 CONTAINER LABEL (FOR BLISTERS GO TO UNIT-DOSE BLISTERS) (C6)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Container meets the too small exemption [21 CFR 201.10(i)]. Please enter Reviewer/Deficiency Comments if you select Deficiency.
ESTABLISHED/PROPRIETARY NAME and STRENGTH:		
☐	☒	Tall Man lettering complies with recommendations found on FDA webpage .
☐	☒	Established/proprietary name and strength are the most prominent information on the Principal Display Panel.
☐	☒	No intervening text (written, printed, or graphic matter) between established name and strength.
THE FOLLOWING COMPONENTS ARE PROPERLY DISPLAYED:		
☐	☒	Net quantity statement. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Dosage statement.
☐	☒	NDC number : prominence, linear bar code, and its orientation.
☐	☒	Expiration date and lot number (or placeholder).
☐	☒	Equivalency statement (product strength).
☐	☒	Medication Guide Pharmacist instructions [21 CFR 208.24(d)].
☐	☒	Controlled Substance Symbol .

Deficiency	No Deficiency	
☐	☒	Image of drug product represents the true size, color, and imprint.
☐	☒	Yellow #5 (tartrazine) warning statement is properly displayed.
☐	☒	Alcohol is properly listed [21 CFR 201.10(d)(2)] .
☐	☒	Latex warning statement is properly displayed [21 CFR 801.437.] .
☐	☒	Gluten statement is appropriately stated.
PRODUCT DIFFERENTIATION:		
☐	☒	ANDA is the same color as the RLD labels as required (e.g. warfarin, levothyroxine, enoxaparin). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Multiple strengths are differentiated by use of different color or other acceptable means.
☐	☒	Labels of proposed product is differentiated from related products .
STORAGE, DISPENSING, MANUFACTURER, and PACKAGING:		
☐	☒	Storage/dispensing statement is consistent with the How Supplied section of the insert/RLD/USP. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Manufacturer/Distributor/Packager statement is acceptable [21 CFR 201.1(h)(5) or (6)] or 21 CFR 201.1(i)] .
☐	☒	Tamper evident (controlled substances) requirements are met.
☐	☒	Use of child-resistant closure (CRC) or non-CRC is appropriate. Describe container closure , cite source, and any issues in Reviewer Comments below.
OVERALL ASSESSMENT:		
☐	☒	Requirements met for the required label statements (21 CFR 201.15 and 21 CFR 201.100). Please enter Reviewer/Deficiency Comments if you select Deficiency.
Reviewer Comments: The 10/30/2019 container labels were determined adequate. Those labels will be attached to this review for completeness.		
Deficiency Comments:		

5.3 PRESCRIBING INFORMATION (C6)

Reviewer Assessment:

Deficiency	No Deficiency	
HIGHLIGHTS:		
☐	☒	Contact information for applicant and FDA are listed correctly.
☐	☒	Revision date appears at the end of HIGHLIGHTS section (PLR) or end of prescribing information (non-PLR).
DESCRIPTION/INACTIVE INGREDIENTS:		
Appropriate warning/precaution statements for inactive ingredients are present (21 CFR 201) Check only if applicable:		
☐	☒	☒ Sulfite (21 CFR 201.22) ☐ Yellow #5 (Tartrazine) (21 CFR 201.20) ☐ Phenylalanine/aspartame (21 CFR 201.21) ☐ Latex (21 CFR 801.437).
☐	☒	Sterile product statement [21 CFR 201.57(c)(12)(i)(D)].
☐	☒	☒ Alcohol is properly listed [21 CFR 201.10(d)(2)].
☐	☒	☒ Gluten statement is appropriately stated.
☐	☒	Dosage form, pharmacologic/therapeutic class, and route of administration properly listed [21 CFR 201.57(c)(12)(i)(B)] and [21 CFR 201.57(c)(12)(i)(E)] .
HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:		
☐	☒	All submitted labels and labeling are consistent with the HOW SUPPLIED section.

Deficiency	No Deficiency	
☐	☒	Physical description (e.g. scoring, color, imprint, capsule size, nozzle tip, cap color) of the finished product in the HOW SUPPLIED section are appropriately displayed.
☐	☒	NDC numbers are present.
☐	☒	Drug product is the same color as the RLD's drug product as required (e.g. warfarin, levothyroxine, enoxaparin).
☐	☒	Storage or dispensing statement is acceptable compared to the RLD/USP monograph. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	"Discard unused portion" for single-dose products.
☐	☒	Manufacturer/Distributor/Packager statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
REGULATORY/OVERALL ASSESSMENT:		
☐	☒	STIC requirements addressed appropriately.
☐	☒	Intent to join the Antiretroviral Pregnancy Registry (APR) upon full approval.
☐	☒	Pregnancy registry information is appropriately included/excluded as required for the RLD.
☒	☐	Patent/exclusivity carve out is acceptable. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Dosage form/strength carve out (RLD combined labeling): justification for retaining information for safety/efficacy.
☐	☒	Prescribing information meets formatting requirements [21 CFR 201.57] (PLR) or 21 CFR 201.80 (non-PLR)].
☐	☒	Prescribing Information is the same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8) . Please enter Reviewer/Deficiency Comments if you select Deficiency.
Reviewer Comments: C5 FTR: In the previous review, we noted that (b)(4) (b)(4) (b)(4) We found this acceptable. (b)(4)		
RLD ANDA (b)(4)		
C6- 6/28/2024 Assessment: Inadequate (b)(4) (b)(4)		
Proposed Prescribing information submitted 5/2/2024 is inadequate. Additionally, the 7.9.2024 Policy CP disclaimer language will be issued for inadequate assessment.		

Deficiency Comments: Deficiency # 1 Created in C6 Prescribing Information Response / Assessment:	HIGHLIGHTS, DOSAGE AND ADMINISTRATION, 3rd bullet in RLD labeling, (b)(4)
Deficiency # 2 Created in C6 Prescribing Information Response / Assessment:	INDICATIONS AND USAGE, 1.1 Adult Heart Failure, 2nd paragraph revise to read as follows: "Left ventricular ejection fraction (LVEF) is a variable measure..." [Note-include the wording for the acronym "LVEF".]
Deficiency # 3 Created in C6 Prescribing Information Response / Assessment:	Geriatric Use, Section 8.5, Revise first paragraph to read as follows (b)(4) (b)(4) Geriatric Use "There were 4,143 heart failure patients 65 years of age and older in PARADIGM-HF [see Clinical Studies (14)]. Of the total number of sacubitril and valsartan-treated patients, 2,087 (49.6%) were 65 years of age and older, while 786 (18.7%) were 75 years of age and older in PARADIGM-HF. No overall differences in safety or effectiveness of sacubitril and valsartan have been observed between patients 65 years of age and older and younger adult patients." No relevant pharmacokinetic differences...
Deficiency # 4 Created in C6 General Comments	We note that on September 12, 2022, Novartis Pharmaceuticals Corporation (Novartis) submitted a citizen petition (Docket No. FDA-2022-P-2228) requesting, among other things, that FDA refrain from approving any ANDA relying on NDA 207620 for Entresto as the reference listed drug until after the expiration of the following patents 1) U.S. Patent Nos. 9,517,226; 9,937,143; and 11,135,192, each expiring on August 22, 2033, and each listed in the Orange Book with the patent use code "U-3084: (Treatment of Heart Failure With Preserved Ejection Fraction)" and (2) U.S. Patent No. 11,058,667 listed in the Orange Book, expiring May 9, 2036, and listed with the patent use code U-3170 (treating chronic heart failure with reduced ejection fraction in patients not taking an ace inhibitor or an ARB or previously taking low doses of these agents, by titrating up from half the usually recommended starting dose). The issues raised by that petition are under review by the agency and FDA has not made a final decision on the issues the petition raises. Nonetheless, in

the interest of expediting processing of your ANDA in the event FDA concludes that applicants may carve out protected labeling, with this communication we are providing you with our current thinking about the labeling for your ANDA with the uses protected by patent s for which you have provided section viii statement s carved out of the label. These deficiency comments included in this communication/email reflect only our current thinking on ANDA labeling were FDA to determine that a labeling carve-out is possible, and this communication/email does not represent a final decision by the agency on the issues raised in the pending citizen petition. As such, additional changes to the proposed labeling of an ANDA for sacubitril and valsartan tablets may be required as the Agency continues to consider issues raised by this petition and Orange Book-listed patents.

Response / Assessment:

5.4 OTHER PATIENT LABELING (C6)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Other patient labeling is the same as the model labeling except for allowable differences. Please enter Reviewer/Deficiency Comments if you select Deficiency.
Reviewer Comments: C6 Assessment on 6/28/2024- Adequate (b)(4) Patient leaflet submitted 5/2/2024 is adequate.		
Deficiency Comments:		

6 COMMENTS/CONSULTS FOR OTHER DISCIPLINES (C6)

A labeling statement required verification from another division discipline. Check only if applicable.

Reviewer Assessment:

☐	Rubber
☐	Latex
☐	Gluten
☐	Alcohol (ethanol)
☐	Aluminum (small/large volume parenteral and pharmacy bulk package)
☐	Sulfite
☐	Phenylalanine (aspartame) - content calculation
☐	Yellow #5 (tartrazine)
☐	Ghost tablet/capsule (i.e. solid or semi-solid mass in stool)
☐	Other
Describe questions/issue(s) sent to and/or received from other discipline(s) (e.g., OPQ, OB): (For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue)	

DELETED PAGES INFORMATION SHEET

IT IS NOT REASONABLE TO SEGREGATE MEANINGFUL PORTIONS OF THE RECORD FOR RELEASE.

INFORMATION HAS BEEN WITHHELD IN ITS ENTIRETY IN ACCORDANCE WITH THE FOLLOWING EXEMPTIONS(S):

(b) (4)

5 U.S.C. 552 (b) (4) - trade secrets and commercial or financial information obtained from a person and privileged or confidential.



Burhan
Nour

Digitally signed by Burhan Nour
Date: 7/12/2024 12:20:00PM
GUID: 508da70600028ae6e75df33aa0f5b2ce



Angela
Payne

Digitally signed by Angela Payne
Date: 7/12/2024 06:19:44AM
GUID: 508da70600028ab611d2ba935d5074a6

Labeling Review

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	March 7, 2024
ANDA Number(s)	213748
Review Number	5
Applicant Name	MSN Laboratories Private Limited
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Sacubitril and Valsartan Tablets, 24 mg/26 mg, 49 mg /51 mg and 97 mg/103 mg
Proposed Proprietary Name	None
Submission Received Date	December 27, 2022
Primary Labeling Reviewer	Wan Lee
Secondary Labeling Reviewer	Betty Turner
Review Conclusion ☐ Acceptable - No Comments ☐ Acceptable - Include Post Approval Comments ☒ Minor Deficiency* - Refer to Labeling Deficiencies and Comments for Letter to Applicant ☐ Major Deficiency** - Refer to Labeling Deficiencies and Comments for Letter to Applicant *Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.	
On Policy Alert List	☒ Yes ☐ No
Acceptable For Filing	☒ Yes ☐ No
Combined Insert/Outsert	☐ Yes ☒ No

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1 **LABELING COMMENTS (C5)**

1.1 **LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT (C5)**

The following comments have been identified by the Division of Labeling Review (DLR) based on your submission(s) on December 27, 2022.

Prior to final approval, the proposed labeling should be clear and precise (grammar, spelling, and formatting) for end users, and accurately reflect the Reference Listed Drug (RLD) information to comply with FDA policies, laws, regulations (i.e., 21 CFR 314.94(a)(8)), official compendia, and relevant guidance.

1. GENERAL COMMENTS

a.

(b)(4)

- b. We note that on September 12, 2022, Novartis Pharmaceuticals Corporation (Novartis) submitted a citizen petition (Docket No. FDA-2022-P-2228) requesting, among other things, that FDA refrain from approving any ANDA relying on NDA 207620 for Entresto as the reference listed drug until after the expiration of the following patents 1) U.S. Patent Nos. 9,517,226; 9,937,143; and 11,135,192, each expiring on August 22, 2033, and each listed in the Orange Book with the patent use code "U-3084: (Treatment of Heart Failure With Preserved Ejection Fraction)" and (2) U.S. Patent No. 11,058,667 listed in the Orange Book, expiring May 9, 2036, and listed with the patent use code U-3170 (treating chronic heart failure with reduced ejection fraction in patients not taking an ace inhibitor or an ARB or previously taking low doses of these agents, by titrating up from half the usually recommended starting dose). In this complete response letter, we have included only comments that are unrelated to the citizen petition issues (FDA-2022-P-2228). Per Section XI, paragraph E of the GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2023-2027 ("GDUFA III Commitment Letter"), a response that addresses all other issues unrelated to the citizen petition is still considered a complete response. Since the citizen petition raises labeling issues that would delay only part of a complete response, we are including only comments unrelated to the pending citizen petition until a citizen response has been finalized. Additional changes to the proposed labeling of an ANDA for sacubitril and valsartan tablets may be required as the Agency continues to consider issues raised by this petition and Orange Book-listed patents.

We also note that on April 18, 2019, Novartis submitted a citizen petition to FDA (Docket No. FDA-2019-P-1893) requesting that FDA require ANDAs that reference ENTRESTO (sacubitril and valsartan) tablets to demonstrate active pharmaceutical ingredient (API) sameness based on the chemical structure of the sacubitril and valsartan active ingredients present in the finished dosage form; revise FDA's draft product-specific guidance (PSG) on sacubitril and valsartan oral tablets to recommend API sameness be established by showing that the chemical structure of each API in the finished dosage form of a proposed generic is identical to the chemical structure of each API in the RLD; and further revise the PSG to include other criteria.

The issues raised by these citizen petitions are currently under review by the Agency, and FDA has not made a final decision on the issues the petitions raise. The comments included in this communication reflect only our current thinking, and this communication does not represent a final decision by the Agency on the issues raised in the pending citizen petitions.

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book (OB), and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE (C5)

1.3 POST-APPROVAL REVISIONS (C5)

These comments will be addressed post approval (in the first labeling supplement review).

2 INSTRUCTIONS FOR ASSESSMENT (C5)

General Comments:

Select the "no deficiency" or "deficiency" radio button as appropriate for each row. If a "Deficiency Comments" appears, ensure it is appropriate for your situation, edit, or enter "Reviewer Comments" if necessary.

If there is no issue/concern, or if the question is not applicable. No "Deficiency Comments" will appear but reviewers can still enter "Reviewer Comments" if desired.

☐	☒	There is information in the Orange Book that the applicant needs to address.
☒	☐	Information in the Orange Book has expired and the applicant needs to revise labeling.

Reviewer Comments:

Enter free text in this section as necessary.

Deficiency Comments:

- Standardized comments/deficiencies are available for certain questions. For a complete list of standardized comments, reference the [DLR Standardized Comments](#) SharePoint.
- Reviewers can modify standardized comments/deficiencies for their situation.

- Deficiencies will have a review number, deficiency number, and roman numeral in the user interface. For first original reviews the review number and iteration numeral will align; however, older reviews may have review numbers and iteration numerals that differ due to some reviews being completed under past practices.
- Deficiency comments will populate by default to the Labeling Comments deficiency section unless you select the Post-Approval checkbox. Assessors also have the option to move all comments to the Post-Approval Revisions section or vice versa from the Labeling Comments tab.

The screenshot shows a web interface for 'Deficiency Comments'. It features a table with the following columns: 'Creation Cycle', 'Category', 'Deficiency', 'Response/Assessment', and 'Post-Approval'. The 'Creation Cycle' column has a dropdown menu with 'C1' selected. The 'Category' column has a dropdown menu with 'Select...' selected. The 'Deficiency' column contains a text area with 'Normal Text' and some icons. The 'Response/Assessment' column is empty. The 'Post-Approval' column has a checkbox labeled 'Post-Approval'. A red arrow points from the 'Deficiency' column to the 'Post-Approval' checkbox. There is also a 'Add Deficiency' button at the bottom left.

3 OVERALL ASSESSMENT OF MATERIALS REVIEWED (C5)

Table 1: Review Summary of Container Label and Carton Labeling

	Final or Draft or NA	Packaging Sizes	Submission Received Date	Recommendation
Container	Final	24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg (60s and 180s count bottles)	10/30/2019	Satisfactory
Blister	N/A	N/A		
Carton	N/A	N/A		

Table 2: Review Summary of Prescribing Information and Patient Labeling

	Final or Draft or NA	Revision Date and/or Code	Submission Received Date	Recommendation
Prescribing Information	Draft	12/2022	12/27/2022	Revise
Medication Guide	N/A	N/A		
Patient Information	Draft	12/2022	12/27/2022	Revise
Instructions for Use	N/A	N/A		
SPL Data Elements				

4 LABELING REVIEW INFORMATION(C5)

4.1 REGULATORY INFORMATION (C5)

Yes	No	
☒	☐	Are there any applicable issues in DLR's SharePoint Drug Facts ?
		12/12/2021

Yes	No	
		(b)(4) 3/11/2024 CP Disclaimer Language (Updated via email OGD) <i>We note that on September 12, 2022, Novartis Pharmaceuticals Corporation (Novartis) submitted a citizen petition (Docket No. FDA-2022-P-2228) requesting, among other things, that FDA refrain from approving any ANDA relying on NDA 207620 for Entresto as the reference listed drug until after the expiration of the following patents 1) U.S. Patent Nos. 9,517,226; 9,937,143;</i>

Yes	No																			
		and 11,135,192, each expiring on August 22, 2033, and each listed in the Orange Book with the patent use code "U-3084: (Treatment of Heart Failure With Preserved Ejection Fraction)" and (2) U.S. Patent No. 11,058,667 listed in the Orange Book, expiring May 9, 2036, and listed with the patent use code U-3170 (treating chronic heart failure with reduced ejection fraction in patients not taking an ace inhibitor or an ARB or previously taking low doses of these agents, by titrating up from half the usually recommended starting dose). In this complete response letter, we have included only comments that are unrelated to the citizen petition issues (FDA-2022-P-2228). Per Section XI, paragraph E of the GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2023-2027 ("GDUFA III Commitment Letter"), a response that addresses all other issues unrelated to the citizen petition is still considered a complete response. Since the citizen petition raises labeling issues that would delay only part of a complete response, we are including only comments unrelated to the pending citizen petition until a citizen response has been finalized. Additional changes to the proposed labeling of an ANDA for sacubitril and valsartan tablets may be required as the Agency continues to consider issues raised by this petition and Orange Book-listed patents. We also note that on April 18, 2019, Novartis submitted a citizen petition to FDA (Docket No. FDA-2019-P-1893) requesting that FDA require ANDAs that reference ENTRESTO (sacubitril and valsartan) tablets to demonstrate active pharmaceutical ingredient (API) sameness based on the chemical structure of the sacubitril and valsartan active ingredients present in the finished dosage form; revise FDA's draft product-specific guidance (PSG) on sacubitril and valsartan oral tablets to recommend API sameness be established by showing that the chemical structure of each API in the finished dosage form of a proposed generic is identical to the chemical structure of each API in the RLD; and further revise the PSG to include other criteria. The issues raised by these citizen petitions are currently under review by the Agency, and FDA has not made a final decision on the issues the petitions raise. The comments included in this communication reflect only our current thinking, and this communication does not represent a final decision by the Agency on the issues raised in the pending citizen petitions. Since our review is inadequate, this will be added as a deficiency comment in our review.																		
☒	☐	Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? <table border="1"> <tr> <td>CP</td> <td>FDA-2022-P-2228</td> <td>Entresto</td> <td>sacubitril valsartan tablets</td> <td> Petition requests that the FDA refrain from approving an ANDA relying on ENTRESTO NDA 207620 at least until after the expiration of the 3-year exclusivity in February 2024. Upon expiration of the 3-year exclusivity period, an ANDA applicant would be required to submit a patent certification to the HfPEF Patents. For the reasons described above, an ANDA applicant cannot submit a section viii statement and labeling that proposes to omit the patented use in HfPEF patients. In addition, the approved labeling for ENTRESTO describes a modified dosing regimen for patients who are not taking an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB), or who were previously taking low doses of these agents. </td> <td>207620</td> </tr> <tr> <td colspan="3"> No Approval Actions (TA/AP) can be taken prior to contacting Policy Lead </td> <td colspan="2"> No CRL can be issued prior to contacting Policy Lead; No CC/IR/DRL related to Nitrosamines can be issued prior to contacting Policy Lead </td> <td> Please contact Policy Lead for disclaimer language prior to issuing CRL. Please contact policy lead before approving any ANDA referencing Entresto for documentation re patent- and exclusivity-related labeling/carve-out issues. </td> </tr> <tr> <td colspan="5"></td> <td> 9/13/2022 Ariana Figueroa </td> </tr> </table>	CP	FDA-2022-P-2228	Entresto	sacubitril valsartan tablets	Petition requests that the FDA refrain from approving an ANDA relying on ENTRESTO NDA 207620 at least until after the expiration of the 3-year exclusivity in February 2024. Upon expiration of the 3-year exclusivity period, an ANDA applicant would be required to submit a patent certification to the HfPEF Patents. For the reasons described above, an ANDA applicant cannot submit a section viii statement and labeling that proposes to omit the patented use in HfPEF patients. In addition, the approved labeling for ENTRESTO describes a modified dosing regimen for patients who are not taking an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB), or who were previously taking low doses of these agents.	207620	No Approval Actions (TA/AP) can be taken prior to contacting Policy Lead			No CRL can be issued prior to contacting Policy Lead; No CC/IR/DRL related to Nitrosamines can be issued prior to contacting Policy Lead		Please contact Policy Lead for disclaimer language prior to issuing CRL. Please contact policy lead before approving any ANDA referencing Entresto for documentation re patent- and exclusivity-related labeling/carve-out issues.						9/13/2022 Ariana Figueroa
CP	FDA-2022-P-2228	Entresto	sacubitril valsartan tablets	Petition requests that the FDA refrain from approving an ANDA relying on ENTRESTO NDA 207620 at least until after the expiration of the 3-year exclusivity in February 2024. Upon expiration of the 3-year exclusivity period, an ANDA applicant would be required to submit a patent certification to the HfPEF Patents. For the reasons described above, an ANDA applicant cannot submit a section viii statement and labeling that proposes to omit the patented use in HfPEF patients. In addition, the approved labeling for ENTRESTO describes a modified dosing regimen for patients who are not taking an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB), or who were previously taking low doses of these agents.	207620															
No Approval Actions (TA/AP) can be taken prior to contacting Policy Lead			No CRL can be issued prior to contacting Policy Lead; No CC/IR/DRL related to Nitrosamines can be issued prior to contacting Policy Lead		Please contact Policy Lead for disclaimer language prior to issuing CRL. Please contact policy lead before approving any ANDA referencing Entresto for documentation re patent- and exclusivity-related labeling/carve-out issues.															
					9/13/2022 Ariana Figueroa															

4.2 MODEL PRESCRIBING INFORMATION (C5)

Table 3: Review Model Labeling for Prescribing Information/Patient Labeling
(Check the box used as the Model Labeling)

☒ MOST RECENTLY APPROVED NDA MODEL LABELING

Table 3: Review Model Labeling for Prescribing Information/Patient Labeling
(Check the box used as the Model Labeling)

(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so, enter the most recently approved ANDA labeling information as applicable.)

NDA#/Supplement# (S-000 if original): NDA207620 / S-018

Supplement Approval Date: 02/16/2021

Proprietary Name: Entresto

Established Name: sacubitril and valsartan tablets

Description of Supplement:

This Prior Approval supplemental new drug application 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.

2/16/2021 RPM Review

Proposed Indication in original supplemental submission: to reduce worsening heart failure (total heart failure hospitalizations and urgent heart failure visits) in patients with chronic heart failure and preserved ejection fraction

Amended Proposed Indication in original submission: to reduce worsening heart failure (total heart failure hospitalizations and urgent heart failure visits) in patients with chronic heart failure and preserved ejection fraction **with left ventricular ejection fraction (LVEF) below normal.**

Final indication: 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.

LVEF is a variable measure, so use clinical judgment in deciding whom to treat

Entresto was also being studied in patients with preserved ejection fraction (HFpEF). The pivotal trial known as **PARAGON-HF** was a double-blind randomized clinical trial comparing Entresto 200 mg BID to Valsartan 160 mg BID. Eligible patients had symptomatic HFpEF (NYHA class II-IV) with LVEF $\geq$ 45% requiring diuretics. Other entry criteria were left ventricular hypertrophy (LVH) or left atrial enlargement (LAE), and elevated N-terminal-proB-type natriuretic peptide (NT-proBNP). The primary efficacy endpoint was a composite of total (first and recurrent) hospitalizations for heart failure and cardiovascular death. Secondary endpoints were NYHA class, KCCQ, renal composite outcome and all-cause mortality. The trial fell short of meeting statistical significance, but the Division suggested that the data might support a new claim. **This supplement was submitted proposing a new indication to include HFpEF patients.**

Link:

<https://panorama.fda.gov/document/preview?versionID=653012c0022c4736e3bce382ed9128a9&ID=652f19fc0212ed0c9b4b18829b287311>

☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING**

☒ **OTHER/TEMPLATE (e.g., Pending Supplements, BPCA, PREA, Carve-out):**

(b)(4)

Most Recently APPROVED NDA:

NDA 207620/S-024 approved on 10/18/2023 (CMC Supplement specific to NDA - no impact on subject ANDA)

(b)(4)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	ANDA is up-to-date with the RLD/Model labeling.

Reviewer Comments:
The 12/12/2021 carve-out template was used as our model labeling.

- This model labeling uses the most current NDA labeling with Prescribing Information, S-018, that

(b)(4)
- Note that the most recently approved supplement for the NDA, 207620/S-024, approved on 10/18/2023 provides for changes to the container labels that is specific to the NDA. No impact on the subject ANDA.
-
- (b)(4)

Deficiency Comments:

4.3 PATENTS AND EXCLUSIVITIES (C5)

The [Orange Book](#) was searched on 03/07/2024

Table 4 provides Orange Book patents for the Model Labeling (NDA207620) and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 4: Impact of Model Labeling Patents on ANDA Labeling							
Strengths	Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	11058667	05/09/2036	U-3170	TREATING CHRONIC HEART FAILURE WITH REDUCED EJECTION FRACTION IN PATIENTS NOT TAKING AN ACE INHIBITOR OR AN ARB OR PREVIOUSLY TAKING LOW DOSES OF THESE AGENTS, BY TITRATING UP FROM HALF THE USUALLY RECOMMENDED STARTING DOSE	viii	12/22/2021	Carve-out
24 mg;26 mg, 49 mg;51 mg,	11135192	08/22/2033	U-3084	TREATMENT OF HEART FAILURE WITH	viii	12/22/2021	Carve-out

Table 4: Impact of Model Labeling Patents on ANDA Labeling

Strengths	Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
97 mg;103 mg				PRESERVED EJECTION FRACTION			
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	7468390*PED	05/27/2024			IV	03/23/2020	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	8101659	01/15/2025			IV	03/23/2020	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	8101659*PED	07/15/2025			IV	03/23/2020	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	8877938	05/27/2027			IV	03/23/2020	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	8877938*PED	11/27/2027			IV	03/23/2020	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	9388134	11/08/2026	U-1723	TREATMENT OF HEART FAILURE	IV	03/23/2020	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	9388134*PED	05/08/2027			IV	03/23/2020	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	9517226	08/22/2033	U-3084	TREATMENT OF HEART FAILURE WITH PRESERVED EJECTION FRACTION	viii	12/22/2021	Carve-out
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	9937143	08/22/2033	U-3084	TREATMENT OF HEART FAILURE WITH PRESERVED EJECTION	viii	12/22/2021	Carve-out

Table 4: Impact of Model Labeling Patents on ANDA Labeling							
Strengths	Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
				FRACTION			

Table 5 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 5: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling						
Strengths	Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	M-82	02/16/2024	LABELING REVISIONS RELATED TO CLINICAL STUDIES	With respect to the exclusivity code M-82 expiring on February 16, 2024, The proposed labeling for the MSN product does not include information associated with the M-82 exclusivity.	12/22/2021	Expired

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	There is information in the Orange Book that the applicant needs to address.
☒	☐	Information in the Orange Book has expired and the applicant needs to revise labeling.

Reviewer Comments:

(b)(4)

(b)(4)

(b)(4)

(b)(4)

In reference to the CP, the most current deficiency comment disclaimer language (dated 11/16/2022) was drafted between ORP and DLR and will be conveyed to the applicant in this assessment since it remains inadequate. Additionally, based on 4/3/2023 meeting with OGD, it was determined that carving out Patent Use Code U-3170 is an option based on current thinking from OND/ORP because deleting this information will not leave the remaining non-protected use less safe or efficacious. Final confirmation from OGD discussions with ORP and DCN (email on 5/24/2023) confirmed that carve-out of Patent Use Code U-3170 (i.e., section 2.5) is an option.

****Note**, currently we are waiting for OCC to provide feedback on our proposed template (e.g., inclusion of the entire indication to align with the RLD).

Deficiency Comments:

Deficiency # 1

Created in C4

General Comments

We note that on December 1, 2021, Novartis Pharmaceuticals Corporation (Novartis) submitted a citizen petition to FDA (Docket No. FDA-2021-P-1286) requesting that FDA not approve any ANDA referencing NDA 207620 ENTRESTO (sacubitril and valsartan) oral tablets until the expiration of the following patents and exclusivities: 3-year exclusivity period covering the labeling changes approved in the February 2021 supplement, including any ANDA that seeks to add language to, or otherwise revise, the existing indication statement in order to omit the exclusivity-protected use; the expiration of the HFpEF Patents if that ANDA contains a section viii statement to these patents and seeks to omit the patent-protected use in HFpEF patients; and the expiration of the '667 Patent if that ANDA contains a section viii statement and seeks to omit the modified dosing regimen for HFpEF patients not taking an ACE inhibitor or ARB, or who were previously taking low doses of these agents. We also note that on April 18, 2019, Novartis submitted a citizen petition to FDA (Docket No. FDA-2019-P-1893) requesting that FDA require ANDAs that reference ENTRESTO (sacubitril and valsartan) tablets to demonstrate active pharmaceutical ingredient (API) sameness based on the chemical structure of the sacubitril and valsartan active ingredients present in the finished dosage form; revise FDA's draft product-specific guidance (PSG) on sacubitril and valsartan oral tablets to recommend API sameness be established by showing that the chemical structure of each API in the finished dosage form of a proposed generic is identical to the chemical structure of each API in the RLD; and further revise the PSG to include other criteria. The issues raised by these petitions are currently under review by the Agency, and FDA has not made a final decision on the issues the petition raises. The comments included in this communication reflect only our current thinking, and this communication does not

Response / Assessment:	represent a final decision by the Agency on the issues raised in the pending citizen petitions. Response: We acknowledge the agency's comment. Reviewer's Assessment: Acceptable
Deficiency # 2 Created in C5 General Comments Response / Assessment:	(b)(4)
Deficiency # 3 Created in C5 General Comments	We note that on September 12, 2022, Novartis Pharmaceuticals Corporation (Novartis) submitted a citizen petition (Docket No. FDA-2022-P-2228) requesting, among other things, that FDA refrain from approving any ANDA relying on NDA 207620 for Entresto as the reference listed drug until after the expiration of the following patents 1) U.S. Patent Nos. 9,517,226; 9,937,143; and 11,135,192, each expiring on August 22, 2033, and each listed in the Orange Book with the patent use code "U-3084: (Treatment of Heart Failure With Preserved Ejection Fraction)" and (2) U.S. Patent No. 11,058,667 listed in the Orange Book, expiring May 9, 2036, and listed with the patent use code U-3170 (treating chronic heart failure with reduced ejection fraction in patients not taking an ace inhibitor or an ARB or previously taking low doses of these agents, by titrating up from half the usually recommended starting dose). In this complete response letter, we have included only comments that are unrelated to the citizen petition issues (FDA-2022-P-2228). Per Section XI, paragraph E of the GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2023-2027 ("GDUFA III Commitment Letter"), a response that addresses all other issues unrelated to the citizen petition is still considered a complete response. Since the citizen petition raises labeling issues that would delay only part of a complete response, we are including only comments unrelated to the pending citizen petition until a citizen response has been finalized. Additional changes to the proposed labeling of an ANDA for sacubitril and valsartan tablets may be required as the Agency continues to consider issues raised by this petition and Orange Book-listed patents. We also note that on April 18, 2019, Novartis submitted a citizen petition to FDA (Docket No. FDA-2019-P-1893) requesting that FDA require ANDAs that reference ENTRESTO (sacubitril and valsartan) tablets to demonstrate active pharmaceutical ingredient (API) sameness based on the chemical structure of the sacubitril and valsartan active ingredients present in the finished dosage form; revise FDA's draft product-specific guidance (PSG) on sacubitril and valsartan oral tablets to recommend API sameness be established by showing that the chemical structure of each API in the finished dosage form of a proposed generic is identical to the chemical

structure of each API in the RLD; and further revise the PSG to include other criteria.

The issues raised by these citizen petitions are currently under review by the Agency, and FDA has not made a final decision on the issues the petitions raise. The comments included in this communication reflect only our current thinking, and this communication does not represent a final decision by the Agency on the issues raised in the pending citizen petitions.

Response / Assessment:

4.4 UNITED STATES PHARMACOPEIA (USP) (C5)

The [USP](#) was searched on 03/08/2024

Table 6: USP

	YES or NO	Date	Monograph Title (N/A if no monograph)	Packaging and Storage/Labeling Statements (N/A if no monograph)
Currently Official	No		N/A	N/A
Not Yet Official	No		N/A	N/A

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Established name is acceptable with regard to the USP monograph or the RLD's nonproprietary name.
☐	☒	RLD's non-proprietary name is different from USP established name.
☐	☒	USP descriptor is correctly used in the appropriate sections of the prescribing information.
USP RECOMMENDATIONS and/or DIFFERENCES IN TEST METHODS (QUALITY):		
☐	☒	DISSOLUTION: The applicant's dissolution statement is appropriate.
☐	☒	ORGANIC IMPURITIES: Drug product meets USP acceptance criteria for organic impurities.
☐	☒	ASSAY: Drug product meets USP acceptance criteria for assay.
Reviewer Comments: None		
Deficiency Comments:		

4.5 MODEL CONTAINER LABELS (C5)

Model container/carton/blister labels (Source: Drugs@FDA; SUPP-018 approved on 2/16/2021)

3 N
0078-0659-20
8



NDC 0078-0659-20



Entresto®
(sacubitril/valsartan)
tablets

24 mg/26 mg

Rx only
60 Tablets

NOVARTIS

Usual Dosage: See prescribing information.
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.

Keep this and all drugs out of the reach of children.

Mfd. Novartis Farma S.p.A.
Torre Annunziata, 80058, Italy

Dist. by Novartis Pharmaceuticals Corp.
East Hanover, NJ 07936

www.Entresto.com

1-888-ENTRESTO (1-888-368-7378)

© Novartis

300055108 US



3 N
0078-0659-67
3



NDC 0078-0659-67



Entresto®
(sacubitril/valsartan)
tablets

24 mg/26 mg

Rx only
180 Tablets

NOVARTIS

Usual Dosage: See prescribing information.
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.

Keep this and all drugs out of the reach of children.

Mfd. by: Novartis Farma S.p.A.
Torre Annunziata, 80058, Italy

Dist. by: Novartis Pharmaceuticals Corp.
East Hanover, NJ 07936

www.Entresto.com

1-888-ENTRESTO (1-888-368-7378)

© Novartis

300055109 US



N
3 0078-0777-20
9



NDC 0078-0777-20



Entresto®
(sacubitril/valsartan)
tablets

49mg/51mg

Rx only
60 Tablets

NOVARTIS

Usual Dosage: See prescribing information.
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.

Keep this and all drugs out of the reach of children.

Mfd. by: Novartis Farmaceutici S.p.A.
Torre Annunziata, 80058, Italy

Dist. by: Novartis Pharmaceuticals Corp.
East Hanover, NJ 07936

www.Entresto.com

1-888-ENTRESTO (1-888 368-7378)

© Novartis

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3 0078-0777-67
4



NDC 0078-0777-67



Entresto®
(sacubitril/valsartan)
tablets

49mg/51mg

Rx only
180 Tablets

NOVARTIS

Usual Dosage: See prescribing information.
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.

Keep this and all drugs out of the reach of children.

Mfd. by: Novartis Farmaceutici S.p.A.
Torre Annunziata, 80058, Italy

Dist. by: Novartis Pharmaceuticals Corp.
East Hanover, NJ 07936

www.Entresto.com

1-888-ENTRESTO (1-888 368-7378)

© Novartis

300055111 US



Insert screenshot of Labeling portion from drug product review if completed:
Drug Product Review complete

8/9/2023 DP Assessment: Adequate

1.14 Labeling

Labeling & Prescribing Information

DESCRIPTION (Rx insert or Active Ingredient(s), and Inactive Ingredients in DRUG FACTS for OTC):

Is the information accurate? ☒ Yes ☐ No

If "No," explain.

Is the drug product subject of a USP monograph? ☐ Yes ☒ No

If "Yes," does labeling have accurate USP statement in the DESCRIPTION (for Rx) or Other Information section of DRUG FACTS (for OTC)?

☐ Yes ☐ No ☐ Statement not needed

If NO, what is/are the needed statement(s)? _____

HOW SUPPLIED section (Rx insert) or Storage (in DRUG FACTS for OTC)

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Is tamper evident feature provided in the container/closure for the OTC products or Controlled Substance (CII – CIV) products? ☐ Yes ☐ No
☒ N/A (NOT OTC or Controlled Substance)

If "No," explain.

For solid oral drug products, only: drug product length(s) of commercial batch(es):

ANDA Strength	Length (MM)	Imprint Code
24 mg/ 26 mg	10.00 x 4.00	one side debossed with 'M' and other side debossed with 'S1'
49 mg/ 51 mg	13.00 x 5.10	one side debossed with 'M' and other side debossed with 'S2'
97 mg/ 103 mg	15.00 x 5.90	one side debossed with 'M' and other side debossed with 'S3'

Send issue to the Labeling assessor through the Platform with a list of quality-related labeling deficiencies and also record reference number or link for all the issues:

Issue Description	Issue Reference Number or Link

LABELING LIST OF DEFICIENCIES

N/A

4/20/2021 DP Assessment: Inadequate-Minor

R REGIONAL INFORMATION

1.14 Labeling

Labeling & Prescribing Information

DESCRIPTION (Rx insert or Active Ingredient(s), and Inactive Ingredients in DRUG FACTS for OTC):

Is the information accurate? ☒ Yes ☐ No

If "No," explain.

Is the drug product subject of a USP monograph? ☐ Yes ☒ No

If "Yes," does labeling have accurate USP statement in the DESCRIPTION (for Rx) or Other Information section of DRUG FACTS (for OTC)?

☐ Yes ☐ No ☐ Statement not needed

If NO, what is/are the needed statement(s)? _____

HOW SUPPLIED section (Rx insert) or Storage (in DRUG FACTS for OTC)

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Is tamper evident feature provided in the container/closure for the OTC products or Controlled Substance (CII – CIV) products? ☐ Yes ☐ No
☒ N/A (NOT OTC or Controlled Substance)

If "No," explain.

For solid oral drug products, only: drug product length(s) of commercial batch(es):

ANDA Strength	Length (MM)	Imprint Code
24 mg/ 26 mg	10.00 x 4.00	one side debossed with 'M' and other side debossed with 'S1'
49 mg/ 51 mg	13.00 x 5.10	one side debossed with 'M' and other side debossed with 'S2'
97 mg/ 103 mg	15.00 x 5.90	one side debossed with 'M' and other side debossed with 'S3'

Send issue to the Labeling assessor through the Platform with a list of quality-related labeling deficiencies and also record reference number or link for all the issues:

Issue Description	Issue Reference Number or Link

LABELING LIST OF DEFICIENCIES

None

5.1.2 DESCRIPTION (C5)

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section

Model Labeling	The tablet inactive ingredients are microcrystalline cellulose, low-substituted hydroxypropylcellulose, crospovidone, magnesium stearate (vegetable origin), talc, and colloidal silicon dioxide. The film-coat inactive ingredients are hypromellose, titanium dioxide (E 171), Macrogol 4000, talc, and iron oxide red (E 172). The film-coat for the 24 mg of sacubitril and 26 mg of valsartan tablet and the 97 mg of sacubitril and 103 mg of valsartan tablet also contains iron oxide black (E 172). The film-coat for the 49 mg of sacubitril and 51 mg of valsartan tablet contains iron oxide yellow (E 172).
Previous ANDA Labeling	The tablet inactive ingredients are colloidal silicon dioxide, crospovidone, croscarmellose sodium, magnesium stearate, microcrystalline cellulose and talc. The film-coat inactive ingredients are hypromellose, titanium dioxide, macrogol, talc and iron oxide red. The film-coat for the 24 mg of sacubitril and 26 mg of valsartan tablet and 97 mg of sacubitril and 103 mg of valsartan tablet also contains iron oxide black. The film-coat for the 49 mg of sacubitril and 51 mg of valsartan tablet also contains iron oxide yellow.
Current ANDA Labeling	The tablet inactive ingredients are colloidal silicon dioxide, crospovidone, croscarmellose sodium, magnesium stearate, microcrystalline cellulose and talc. The film-coat inactive ingredients are hypromellose, titanium dioxide, macrogol, talc and iron oxide red. The film-coat for the 24 mg of sacubitril and 26 mg of valsartan tablet and 97 mg of sacubitril and 103 mg of valsartan tablet also contains iron oxide black. The film-coat for the 49 mg of sacubitril and 51 mg of

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section

valsartan tablet also contains iron oxide yellow.

Reviewers Assessment:

Acceptable: No changes noted.

5.1.3 HOW SUPPLIED/STORAGE AND HANDLING (C5)

Table 8: Comparison of Model Labeling to ANDA Labeling

Model Labeling

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. All strengths are packaged in bottles as described below.

Tablet	Color	Debossment	NDC # 0078-XXXX-XX	
Sacubitril/Valsartan		"NVR" and	Bottle of 60	Bottle of 180
24 mg/26 mg	Violet white	LZ	0659-20	0659-67
49 mg/51 mg	Pale yellow	L1	0777-20	0777-67
97 mg/103 mg	Light pink	L11	0696-20	0696-67

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.

Previous ANDA Labeling

Sacubitril/valsartan tablets are available as unscored, oval shaped, 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. All strengths are packaged in bottles as described below.

Tablet	Color	Debossment	NDC # 69539-XXX-XX	
Sacubitril/Valsartan		"M" and	Bottle of 60	Bottle of 180
24 mg/26 mg	Purple	S1	166-60	166-18
49 mg/51 mg	Light yellow	S2	167-60	167-18
97 mg/103 mg	Light pink	S3	168-60	168-18

Store at 25°C (77°F), excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from moisture.

Current ANDA Labeling

Sacubitril/valsartan tablets are available as unscored, oval shaped, 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. All strengths are packaged in bottles as described below.

Tablet	Color	Debossment	NDC # 69539-XXX-XX	
Sacubitril/Valsartan		"M" and	Bottle of 60	Bottle of 180
24 mg/26 mg	Purple	S1	166-60	166-18
49 mg/51 mg	Light yellow	S2	167-60	167-18
97 mg/103 mg	Light pink	S3	168-60	168-18

Table 8: Comparison of Model Labeling to ANDA Labeling

	Store at 25°C (77°F), excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from moisture. Reviewers Assessment: Acceptable: No changes noted. We do note that the RLD has a slightly different storage temperature. (b)(4) (b)(4) Additionally, the DP assessor found this adequate. Refer to the HOW SUPPLIED section of their review in section 5.1.1 above.
--	---

5.1.4 MANUFACTURER, DISTRIBUTOR, AND/OR PACKER (C5)

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements

Previous ANDA Labeling	
Name and Address on ANDA Prescribing Information	Manufactured by: MSN Laboratories Private Limited Telangana – 509 228, INDIA Distributed by: MSN Pharmaceuticals Inc. Piscataway, NJ 08854 -3714 Issued on: 12/2021
Current ANDA Labeling	
Name and Address on ANDA Prescribing Information	Manufactured by: MSN Laboratories Private Limited Telangana – 509 228, INDIA Distributed by: MSN Pharmaceuticals Inc. Piscataway, NJ 08854 -3714 Issued on: 12/2022 Reviewers Assessment: Acceptable: No changes noted except for updated revision date.

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements

Manufactured by	Manufactured for	Distributed by	Distributed for
-----------------	------------------	----------------	-----------------

5.2 CONTAINER LABEL (FOR BLISTERS GO TO UNIT-DOSE BLISTERS) (C5)**Reviewer Assessment:**

Deficiency	No Deficiency	
☐	☒	Container meets the too small exemption [21 CFR 201.10(i)]. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Deficiency	No Deficiency	
ESTABLISHED/PROPRIETARY NAME and STRENGTH:		
☐	☒	Tall Man lettering complies with recommendations found on FDA webpage .
☐	☒	Established/proprietary name and strength are the most prominent information on the Principal Display Panel.
☐	☒	No intervening text (written, printed, or graphic matter) between established name and strength.
THE FOLLOWING COMPONENTS ARE PROPERLY DISPLAYED:		
☐	☒	Net quantity statement. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Dosage statement.
☐	☒	NDC number : prominence, linear bar code, and its orientation.
☐	☒	Expiration date and lot number (or placeholder).
☐	☒	Equivalency statement (product strength).
☐	☒	Medication Guide Pharmacist instructions [21 CFR 208.24(d)] .
☐	☒	Controlled Substance Symbol .
☐	☒	Image of drug product represents the true size, color, and imprint.
☐	☒	Yellow #5 (tartrazine) warning statement is properly displayed.
☐	☒	Alcohol is properly listed [21 CFR 201.10(d)(2)] .
☐	☒	Latex warning statement is properly displayed [21 CFR 801.437.] .
☐	☒	Gluten statement is appropriately stated.
PRODUCT DIFFERENTIATION:		
☐	☒	ANDA is the same color as the RLD labels as required (e.g. warfarin, levothyroxine, enoxaparin). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Multiple strengths are differentiated by use of different color or other acceptable means.
☐	☒	Labels of proposed product is differentiated from related products .
STORAGE, DISPENSING, MANUFACTURER, and PACKAGING:		
☐	☒	Storage/dispensing statement is consistent with the How Supplied section of the insert/RLD/USP. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Manufacturer/Distributor/Packager statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)] .
☐	☒	Tamper evident (controlled substances) requirements are met.
☐	☒	Use of child-resistant closure (CRC) or non-CRC is appropriate. Describe container closure , cite source, and any issues in Reviewer Comments below.
OVERALL ASSESSMENT:		
☐	☒	Requirements met for the required label statements (21 CFR 201.15 and 21 CFR 201.100). Please enter Reviewer/Deficiency Comments if you select Deficiency.
Reviewer Comments: The 10/30/2019 container labels were determined adequate. Those labels will be attached to this review for completeness.		
Deficiency Comments:		

5.3 PRESCRIBING INFORMATION (C5)

Reviewer Assessment:

Deficiency	No Deficiency	
HIGHLIGHTS:		
☐	☒	Contact information for applicant and FDA are listed correctly.
☐	☒	Revision date appears at the end of HIGHLIGHTS section (PLR) or end of prescribing information (non-PLR).

Deficiency	No Deficiency	
DESCRIPTION/INACTIVE INGREDIENTS:		
☐	☒	Appropriate warning/precaution statements for inactive ingredients are present (21 CFR 201) Check only if applicable: ☒ Sulfite (21 CFR 201.22) ☐ Yellow #5 (Tartrazine) (21 CFR 201.20) ☐ Phenylalanine/aspartame (21 CFR 201.21) ☐ Latex (21 CFR 801.437).
☐	☒	Alcohol is properly listed [21 CFR 201.10(d)(2)].
☐	☒	Gluten statement is appropriately stated.
☐	☒	Sterile product statement [21 CFR 201.57(c)(12)(i)(D)].
☐	☒	Dosage form, pharmacologic/therapeutic class, and route of administration properly listed [21 CFR 201.57(c)(12)(i)(B)] and [21 CFR 201.57(c)(12)(i)(E)].
HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:		
☐	☒	All submitted labels and labeling are consistent with the HOW SUPPLIED section.
☐	☒	Physical description (e.g. scoring, color, imprint, capsule size, nozzle tip, cap color) of the finished product in the HOW SUPPLIED section are appropriately displayed.
☐	☒	NDC numbers are present.
☐	☒	Drug product is the same color as the RLD's drug product as required (e.g. warfarin, levothyroxine, enoxaparin).
☐	☒	Storage or dispensing statement is acceptable compared to the RLD/USP monograph. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	"Discard unused portion" for single-dose products.
☐	☒	Manufacturer/Distributor/Packager statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
REGULATORY/OVERALL ASSESSMENT:		
☐	☒	STIC requirements addressed appropriately.
☐	☒	Intent to join the Antiretroviral Pregnancy Registry (APR) upon full approval.
☐	☒	Pregnancy registry information is appropriately included/excluded as required for the RLD.
☐	☒	Patent/exclusivity carve out is acceptable. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Prescribing information meets formatting requirements [21 CFR 201.57 (PLR) or 21 CFR 201.80 (non-PLR)].
☒	☐	Prescribing Information is the same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8). Please enter Reviewer/Deficiency Comments if you select Deficiency.
Reviewer Comments:		
(b)(4)		
RLD ANDA		
(b)(4)		

Deficiency Comments: Deficiency # 1 Created in C4 Prescribing Information Response / Assessment:	HIGHLIGHTS: i. Indications and Usage: Revise to read, "to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure and reduced ejection fraction (1.1).". (b)(4) Response: i. We acknowledge agency's comment. In accordance to the agency comment, we have revised to read, "to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure and reduced ejection fraction (1.1)." In Indications and Usage under HIGHLIGHTS of PRESCRIBING INFORMATION. (b)(4) Reviewer's Assessment: Acceptable based on the thinking at the time.
Deficiency # 2 Created in C4 Prescribing Information Response / Assessment:	INDICATIONS AND USAGE: i. Revise to read, "Sacubitril and valsartan is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure and reduced ejection fraction.". ii. Retain the sentence, "LVEF is a variable measure, so use clinical judgment in deciding whom to treat [<i>see Clinical Studies (14.1)</i>].". Response: i. We acknowledge agency's comment. In accordance to the agency comment, we have revised to read, "Sacubitril and valsartan is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure and reduced ejection fraction" in INDICATIONS AND USAGE under PRESCRIBING INFORMATION. ii. We acknowledge agency's comment. In accordance to the agency comment, we have retained the sentence, "LVEF is a variable measure, so use clinical judgment in deciding whom to treat [<i>see Clinical Studies (14.1)</i>]" in INDICATIONS AND USAGE under PRESCRIBING INFORMATION. Reviewer's Assessment: Acceptable based on the thinking at the time.
Deficiency # 3 Created in C4 Prescribing Information	(b)(4)

Response / Assessment:	(b)(4)
	Reviewer's Assessment: Acceptable
Deficiency # 4 Created in C4 Prescribing Information Response / Assessment:	(b)(4)
	(b)(4)
	Reviewer's Assessment: Acceptable

5.4 OTHER PATIENT LABELING (C5)

Reviewer Assessment:

Deficiency	No Deficiency	
☒	☐	Other patient labeling is the same as the model labeling except for allowable differences. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

With the expiration of the exclusivities, NPP and M-82 expired 4/1/2023 and 2/16/2024, respectively, information will now need to be retained. Refer to section 4.2 above and deficiency comment associated with the retention of information and removal of disclaimers due to the expiration of the exclusivities.

Deficiency Comments:

Deficiency # 1

Created in C4

Patient Information Leaflet
Response / Assessment:

At the end of the list of inactive ingredients, include, "Prepared sacubitril and valsartan oral suspension also contains Ora-Sweet SF® and Ora-Plus.®". Additionally, include the disclaimer, "All brand names listed are the registered trademarks of their respective owners. ".

Response:

We acknowledge agency's comment. In accordance to the agency comment, we have included "Prepared sacubitril and valsartan oral suspension also contains Ora-Sweet SF® and Ora-Plus.®". Additionally, included the disclaimer, "All brand names listed are the registered trademarks of their respective owners" at the end of the list of inactive ingredients in PATIENT INFORMATION LEAFLET.

Reviewer's Assessment:
Acceptable

6 COMMENTS/CONSULTS FOR OTHER DISCIPLINES (C5)

A labeling statement required verification from another division discipline. Check only if applicable.

Reviewer Assessment:

☐	Rubber
☐	Latex
☐	Gluten
☐	Alcohol (ethanol)
☐	Aluminum (small/large volume parenteral and pharmacy bulk package)
☐	Sulfite
☐	Phenylalanine (aspartame) - content calculation
☐	Yellow #5 (tartrazine)
☐	Ghost tablet/capsule (i.e. solid or semi-solid mass in stool)
☐	Other

Describe questions/issue(s) sent to and/or received from other discipline(s) (e.g., OPQ, OB): (For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue)

Reviewer Comments:

(b)(4)

Deficiency Comments:



Wan
Lee

Digitally signed by Wan Lee
Date: 3/19/2024 09:34:14AM
GUID: 582a2cfa001b51dba58dfaf180bcd09a



Betty
Turner

Digitally signed by Betty Turner
Date: 3/19/2024 10:59:06AM
GUID: 508da70600028acef381be737f7836a9

Labeling Review

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	4/04/2022
ANDA Number(s)	213748
Review Number	4
Applicant Name	MSN Laboratories Private Limited
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Sacubitril and Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg
Proposed Proprietary Name	None
Submission Received Date	December 22, 2021
Primary Labeling Reviewer	Wan Lee
Secondary Labeling Reviewer	Betty Turner
Review Conclusion ☐ Acceptable - No Comments ☐ Acceptable - Include Post Approval Comments ☒ Minor Deficiency* - Refer to Labeling Deficiencies and Comments for Letter to Applicant ☐ Major Deficiency** - Refer to Labeling Deficiencies and Comments for Letter to Applicant *Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.	
On Policy Alert List	☒ Yes ☐ No
Acceptable For Filing	☒ Yes ☐ No
Combined Insert/Outsert	☐ Yes ☒ No

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1 **LABELING COMMENTS (C4)**

1.1 **LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT (C4)**

Labeling deficiencies based on your submission received December 22, 2021 :

1. GENERAL COMMENTS

We note that on December 1, 2021, Novartis Pharmaceuticals Corporation (Novartis) submitted a citizen petition to FDA (Docket No. FDA-2021-P-1286) requesting that FDA not approve any ANDA referencing NDA 207620 ENTRESTO (sacubitril and valsartan) oral tablets until the expiration of the following patents and exclusivities: 3-year exclusivity period covering the labeling changes approved in the February 2021 supplement, including any ANDA that seeks to add language to, or otherwise revise, the existing indication statement in order to omit the exclusivity-protected use; the expiration of the HFpEF Patents if that ANDA contains a section viii statement to these patents and seeks to omit the patent-protected use in HFpEF patients; and the expiration of the '667 Patent if that ANDA contains a section viii statement and seeks to omit the modified dosing regimen for HFrEF patients not taking an ACE inhibitor or ARB, or who were previously taking low doses of these agents. We also note that on April 18, 2019, Novartis submitted a citizen petition to FDA (Docket No. FDA-2019-P-1893) requesting that FDA require ANDAs that reference ENTRESTO (sacubitril and valsartan) tablets to demonstrate active pharmaceutical ingredient (API) sameness based on the chemical structure of the sacubitril and valsartan active ingredients present in the finished dosage form; revise FDA's draft product-specific guidance (PSG) on sacubitril and valsartan oral tablets to recommend API sameness be established by showing that the chemical structure of each API in the finished dosage form of a proposed generic is identical to the chemical structure of each API in the RLD; and further revise the PSG to include other criteria. The issues raised by these petitions are currently under review by the Agency, and FDA has not made a final decision on the issues the petition raises. The comments included in this communication reflect only our current thinking, and this communication does not represent a final decision by the Agency on the issues raised in the pending citizen petitions.

2. PRESCRIBING INFORMATION

a. HIGHLIGHTS:

- i. Indications and Usage: Revise to read, "to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure and reduced ejection fraction (1.1).".

ii.

(b)(4)

b. INDICATIONS AND USAGE:

- i. Revise to read, "Sacubitril and valsartan is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure and reduced ejection fraction."
- ii. Retain the sentence, "LVEF is a variable measure, so use clinical judgment in deciding whom to treat [see *Clinical Studies (14.1)*].".

c.

d.

(b)(4)

3. PATIENT INFORMATION LEAFLET

At the end of the list of inactive ingredients, include, "Prepared sacubitril and valsartan oral suspension also contains Ora-Sweet SF® and Ora-Plus.®". Additionally, include the disclaimer, "All brand names listed are the registered trademarks of their respective owners. ".

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book (OB), and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE (C4)

1.3 POST-APPROVAL REVISIONS (C4)

These comments will be addressed post approval (in the first labeling supplement review).

2 INSTRUCTIONS FOR ASSESSMENT (C4)

General Comments:

Select the "no deficiency" or "deficiency" radio button as appropriate for each row. If a "Deficiency Comments" appears, ensure it is appropriate for your situation, edit, or enter "Reviewer Comments" if necessary.

If there is no issue/concern, or if the question is not applicable. No "Deficiency Comments" will appear but reviewers can still enter "Reviewer Comments" if desired.

☐	☒	There is information in the Orange Book that the applicant needs to address.
☒	☐	Information in the Orange Book has expired and the applicant needs to revise labeling.

Reviewer Comments:

Enter free text in this section as necessary.

Deficiency Comments:

- Standardized comments/deficiencies are available for certain questions. For a complete list of standardized comments, reference the [DLR Standardized Comments](#) SharePoint.
- Reviewers can modify standardized comments/deficiencies for their situation.
- Deficiencies will have a review number, deficiency number, and roman numeral in the user interface. For first original reviews the review number and iteration numeral will align; however, older reviews may have review numbers and iteration

numerals that differ due to some reviews being completed under past practices.

- Deficiency comments will populate by default to the Labeling Comments deficiency section unless you select the Post-Approval checkbox. Assessors also have the option to move all comments to the Post-Approval Revisions section or vice versa from the Labeling Comments tab.

The screenshot shows a 'Deficiency Comments' form with tabs for 'Creation Cycle', 'Category', 'Deficiency', 'Response/Assessment', and 'Post-Approval'. The 'Post-Approval' tab is active, and a red arrow points to the 'Post-Approval' checkbox, which is currently unchecked.

3 OVERALL ASSESSMENT OF MATERIALS REVIEWED (C4)

Table 1: Review Summary of Container Label and Carton Labeling

	Final or Draft or NA	Packaging Sizes	Submission Received Date	Recommendation
Container	Final	24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg (60s and 180s count bottles)	10/30/2019	Satisfactory
Blister	N/A	N/A		
Carton	N/A	N/A		

Table 2: Review Summary of Prescribing Information and Patient Labeling

	Final or Draft or NA	Revision Date and/or Code	Submission Received Date	Recommendation
Prescribing Information	Draft	12/2021	12/22/2021	Revise
Medication Guide	N/A	N/A		
Patient Information	Draft	12/2021	12/22/2021	Revise
Instructions for Use	N/A	N/A		
SPL Data Elements				

4 LABELING REVIEW INFORMATION(C4)

4.1 REGULATORY INFORMATION (C4)

Yes	No	
☒	☐	Are there any applicable issues in DLR's SharePoint Drug Facts ?
		(b)(4)
		12/12/2021

DELETED PAGES INFORMATION SHEET

IT IS NOT REASONABLE TO SEGREGATE MEANINGFUL PORTIONS OF THE RECORD FOR RELEASE.

INFORMATION HAS BEEN WITHHELD IN ITS ENTIRETY IN ACCORDANCE WITH THE FOLLOWING EXEMPTIONS(S):

(b) (4)

5 U.S.C. 552 (b) (4) - trade secrets and commercial or financial information obtained from a person and privileged or confidential.

Table 3: Review Model Labeling for Prescribing Information/Patient Labeling
(Check the box used as the Model Labeling)

☒ **MOST RECENTLY APPROVED NDA MODEL LABELING**

(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so, enter the most recently approved ANDA labeling information as applicable.)

NDA#/Supplement# (S-000 if original): NDA207620 / S-018

Supplement Approval Date: 02/16/2021

Proprietary Name: Entresto

Established Name: sacubitril and valsartan tablets

Description of Supplement:

This Prior Approval supplemental new drug application 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.

2/16/2021 RPM Review

Proposed Indication in original supplemental submission: to reduce worsening heart failure (total heart failure hospitalizations and urgent heart failure visits) in patients with chronic heart failure and preserved ejection fraction

Amended Proposed Indication in original submission: to reduce worsening heart failure (total heart failure hospitalizations and urgent heart failure visits) in patients with chronic heart failure and preserved ejection fraction **with left ventricular ejection fraction (LVEF) below normal.**

Final indication: 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.

LVEF is a variable measure, so use clinical judgment in deciding whom to treat

Entresto was also being studied in patients with preserved ejection fraction (HFpEF). The pivotal trial known as **PARAGON-HF** was a double-blind randomized clinical trial comparing Entresto 200 mg BID to Valsartan 160 mg BID. Eligible patients had symptomatic HFpEF (NYHA class II-IV) with LVEF $\geq$ 45% requiring diuretics. Other entry criteria were left ventricular hypertrophy (LVH) or left atrial enlargement (LAE), and elevated N-terminal-proB-type natriuretic peptide (NT-proBNP). The primary efficacy endpoint was a composite of total (first and recurrent) hospitalizations for heart failure and cardiovascular death. Secondary endpoints were NYHA class, KCCQ, renal composite outcome and all-cause mortality. The trial fell short of meeting statistical significance, but the Division suggested that the data might support a new claim. **This supplement was submitted proposing a new indication to include HFpEF patients.**

Link: https://palantir.fda.gov/workspace/hubble/external/object/v0/fda-communication?pk_communication=4747255_4336977_090140af805d2738_NDA207620_3091789

☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING**

☒ **OTHER/TEMPLATE (e.g., Pending Supplements, BPCA, PREA, Carve-out):**

(b)(4)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	ANDA is up-to-date with the RLD/Model labeling.

Reviewer Comments:

(b)(4)

Deficiency Comments:**4.3 PATENTS AND EXCLUSIVITIES (C4)**

The [Orange Book](#) was searched on 04/04/2022

Table 4 provides Orange Book patents for the Model Labeling (NDA207620) and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 4: Impact of Model Labeling Patents on ANDA Labeling

Strengths	Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	11058667	05/09/2036	U-3170	TREATING CHRONIC HEART FAILURE WITH REDUCED EJECTION FRACTION IN PATIENTS NOT TAKING AN ACE INHIBITOR OR AN ARB OR PREVIOUSLY TAKING LOW DOSES OF THESE AGENTS, BY TITRATING UP FROM HALF THE USUALLY RECOMMENDED STARTING DOSE	viii	12/22/2021	Carve-out
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	11135192	08/22/2033	U-3084	TREATMENT OF HEART FAILURE WITH PRESERVED EJECTION FRACTION	viii	12/22/2021	Carve-out
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	7468390	11/27/2023			IV	03/23/2020	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	7468390*PED	05/27/2024			IV	03/23/2020	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	8101659	01/15/2025			IV	03/23/2020	None

Table 4: Impact of Model Labeling Patents on ANDA Labeling

Strengths	Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
mg							
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	8101659*PED	07/15/2025			IV	03/23/2020	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	8404744	01/14/2023			IV	03/23/2020	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	8404744*PED	07/14/2023			IV	03/23/2020	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	8796331	01/14/2023	U-1723	TREATMENT OF HEART FAILURE	IV	03/23/2020	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	8796331*PED	07/14/2023			IV	03/23/2020	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	8877938	05/27/2027			IV	03/23/2020	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	8877938*PED	11/27/2027			IV	03/23/2020	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	9388134	11/08/2026	U-1723	TREATMENT OF HEART FAILURE	IV	03/23/2020	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	9388134*PED	05/08/2027			IV	03/23/2020	None
24 mg;26 mg, 49 mg;51 mg,	9517226	08/22/2033	U-3084	TREATMENT OF HEART FAILURE WITH	viii	12/22/2021	Carve-out

Table 4: Impact of Model Labeling Patents on ANDA Labeling							
Strengths	Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
97 mg;103 mg				PRESERVED EJECTION FRACTION			
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	9937143	08/22/2033	U-3084	TREATMENT OF HEART FAILURE WITH PRESERVED EJECTION FRACTION	viii	12/22/2021	Carve-out

Table 5 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 5: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling						
Strengths	Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	NPP	10/01/2022	NEW PATIENT POPULATION	With respect to the exclusivity code "NPP *PED" expiring on April 01, 2023. The proposed labeling for the MSN product does not include information associated with the NPP*PED exclusivity.	12/22/2021	Carve-out
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	NPP PED	04/01/2023	NEW PATIENT POPULATION; PEDIATRIC EXCLUSIVITY	With respect to the exclusivity code "NPP *PED" expiring on April 01, 2023. The proposed labeling for the MSN product does not include information associated with the	12/22/2021	Carve-out

Table 5: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling

Strengths	Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact
				NPP*PED exclusivity.		
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	M-82	02/16/2024	LABELING REVISIONS RELATED TO CLINICAL STUDIES	With respect to the exclusivity code M-82 expiring on February 16, 2024. The proposed labeling for the MSN product does not include information associated with the M-82 exclusivity.	12/22/2021	Carve-out

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	There is information in the Orange Book that the applicant needs to address.
☐	☒	Information in the Orange Book has expired and the applicant needs to revise labeling.

Reviewer Comments:

(b)(4)

Deficiency Comments:

Deficiency # 1

Created in C4

General Comments

We note that on December 1, 2021, Novartis Pharmaceuticals Corporation (Novartis) submitted a citizen petition to FDA (Docket No. FDA-2021-P-1286) requesting that FDA not approve any ANDA referencing NDA 207620 ENTRESTO (sacubitril and valsartan) oral tablets until the expiration of the following patents and exclusivities: 3-year exclusivity

period covering the labeling changes approved in the February 2021 supplement, including any ANDA that seeks to add language to, or otherwise revise, the existing indication statement in order to omit the exclusivity-protected use; the expiration of the HFpEF Patents if that ANDA contains a section viii statement to these patents and seeks to omit the patent-protected use in HFpEF patients; and the expiration of the '667 Patent if that ANDA contains a section viii statement and seeks to omit the modified dosing regimen for HFpEF patients not taking an ACE inhibitor or ARB, or who were previously taking low doses of these agents. We also note that on April 18, 2019, Novartis submitted a citizen petition to FDA (Docket No. FDA-2019-P-1893) requesting that FDA require ANDAs that reference ENTRESTO (sacubitril and valsartan) tablets to demonstrate active pharmaceutical ingredient (API) sameness based on the chemical structure of the sacubitril and valsartan active ingredients present in the finished dosage form; revise FDA's draft product-specific guidance (PSG) on sacubitril and valsartan oral tablets to recommend API sameness be established by showing that the chemical structure of each API in the finished dosage form of a proposed generic is identical to the chemical structure of each API in the RLD; and further revise the PSG to include other criteria. The issues raised by these petitions are currently under review by the Agency, and FDA has not made a final decision on the issues the petition raises. The comments included in this communication reflect only our current thinking, and this communication does not represent a final decision by the Agency on the issues raised in the pending citizen petitions.

Response / Assessment:

4.4 UNITED STATES PHARMACOPEIA (USP) (C4)

The [USP](#) was searched on 04/04/2022

Table 6: USP

	YES or NO	Date	Monograph Title (N/A if no monograph)	Packaging and Storage/Labeling Statements (N/A if no monograph)
Currently Official	No		N/A	N/A
Not Yet Official	No		N/A	N/A

Reviewer Assessment:

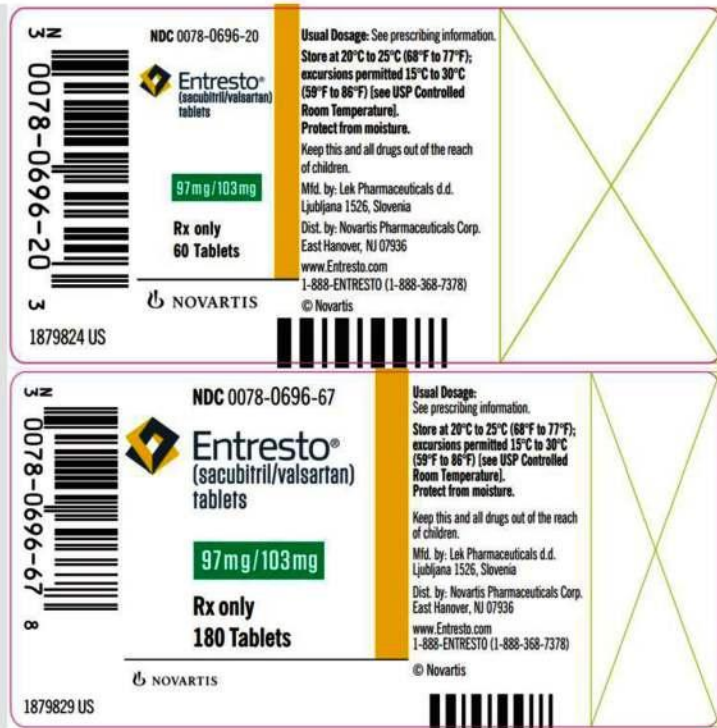
Deficiency	No Deficiency	
☐	☒	Established name is acceptable with regard to the USP monograph or the RLD's nonproprietary name.
☐	☒	RLD's non-proprietary name is different from USP established name.
☐	☒	USP descriptor is correctly used in the appropriate sections of the prescribing information.
USP RECOMMENDATIONS and/or DIFFERENCES IN TEST METHODS (QUALITY):		
☐	☒	DISSOLUTION: The applicant's dissolution statement is appropriate.
☐	☒	ORGANIC IMPURITIES: Drug product meets USP acceptance criteria for organic impurities.

Deficiency	No Deficiency	
☐	☒	ASSAY: Drug product meets USP acceptance criteria for assay.
Reviewer Comments:		
Deficiency Comments:		

4.5 MODEL CONTAINER LABELS (C4)

Model container/carton/blister labels (Source: DARRTS; SUPP-017 approved on 9/10/2020)

3 N 0078-0659-20 8 1879358 US	NDC 0078-0659-20 Entresto® (sacubitril/valsartan) tablets 24 mg/26 mg Rx only 60 Tablets NOVARTIS	Usual Dosage: See prescribing information. Store at 20°C to 25°C (68°F to 77°F); excursions permitted 15°C to 30°C (59°F to 86°F) (see USP Controlled Room Temperature). Protect from moisture. Keep this and all drugs out of the reach of children. Mfd. by: Lek Pharmaceuticals d.d. Ljubljana 1526, Slovenia Dist. by: Novartis Pharmaceuticals Corp. East Hanover, NJ 07936 www.Entresto.com 1-888-ENTRESTO (1-888-368-7378) © Novartis
3 N 0078-0659-67 3 1879360 US	NDC 0078-0659-67 Entresto® (sacubitril/valsartan) tablets 24 mg/26 mg Rx only 180 Tablets NOVARTIS	Usual Dosage: See prescribing information. Store at 20°C to 25°C (68°F to 77°F); excursions permitted 15°C to 30°C (59°F to 86°F) (see USP Controlled Room Temperature). Protect from moisture. Keep this and all drugs out of the reach of children. Mfd. by: Lek Pharmaceuticals d.d. Ljubljana 1526, Slovenia Dist. by: Novartis Pharmaceuticals Corp. East Hanover, NJ 07936 www.Entresto.com 1-888-ENTRESTO (1-888-368-7378) © Novartis
3 N 0078-0777-20 9 1879776 US	NDC 0078-0777-20 Entresto® (sacubitril/valsartan) tablets 49 mg/51 mg Rx only 60 Tablets NOVARTIS	Usual Dosage: See prescribing information. Store at 20°C to 25°C (68°F to 77°F); excursions permitted 15°C to 30°C (59°F to 86°F) (see USP Controlled Room Temperature). Protect from moisture. Keep this and all drugs out of the reach of children. Mfd. by: Lek Pharmaceuticals d.d. Ljubljana 1526, Slovenia Dist. by: Novartis Pharmaceuticals Corp. East Hanover, NJ 07936 www.Entresto.com 1-888-ENTRESTO (1-888-368-7378) © Novartis
3 N 0078-0777-67 4 1879793 US	NDC 0078-0777-67 Entresto® (sacubitril/valsartan) tablets 49 mg/51 mg Rx only 180 Tablets NOVARTIS	Usual Dosage: See prescribing information. Store at 20°C to 25°C (68°F to 77°F); excursions permitted 15°C to 30°C (59°F to 86°F) (see USP Controlled Room Temperature). Protect from moisture. Keep this and all drugs out of the reach of children. Mfd. by: Lek Pharmaceuticals d.d. Ljubljana 1526, Slovenia Dist. by: Novartis Pharmaceuticals Corp. East Hanover, NJ 07936 www.Entresto.com 1-888-ENTRESTO (1-888-368-7378) © Novartis



5 ASSESSMENT OF ANDA LABELING AND LABELS (C4)

5.1 QUALITY INFORMATION (DRUG PRODUCT MOU & BIOPHARMACEUTICS) (C4)

5.1.1 DRUG PRODUCT REVIEW (C4)

Insert screenshot of Labeling portion from drug product review if completed:
Drug Product Review complete

Pre-CRL assessment. Post CRL assessment still pending. However, there are no labeling issues identified.
4/20/2021 DP Assessment: Inadequate-Minor

R REGIONAL INFORMATION

1.14 Labeling

Labeling & Prescribing Information

DESCRIPTION (Rx insert or Active Ingredient(s), and Inactive Ingredients in DRUG FACTS for OTC):

Is the information accurate? ☒ Yes ☐ No

If "No," explain.

Is the drug product subject of a USP monograph? ☐ Yes ☒ No

If "Yes," does labeling have accurate USP statement in the DESCRIPTION (for Rx) or Other Information section of DRUG FACTS (for OTC)?

☐ Yes ☐ No ☐ Statement not needed

If NO, what is/are the needed statement(s)? _____

HOW SUPPLIED section (Rx insert) or Storage (in DRUG FACTS for OTC)

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Is tamper evident feature provided in the container/closure for the OTC products or Controlled Substance (CII – CIV) products? ☐ Yes ☐ No
☒ N/A (NOT OTC or Controlled Substance)

If "No," explain.

For solid oral drug products, only: drug product length(s) of commercial batch(es):

ANDA Strength	Length (MM)	Imprint Code
24 mg/ 26 mg	10.00 x 4.00	one side debossed with 'M' and other side debossed with 'S1'
49 mg/ 51 mg	13.00 x 5.10	one side debossed with 'M' and other side debossed with 'S2'
97 mg/ 103 mg	15.00 x 5.90	one side debossed with 'M' and other side debossed with 'S3'

Send issue to the Labeling assessor through the Platform with a list of quality-related labeling deficiencies and also record reference number or link for all the issues:

Issue Description	Issue Reference Number or Link

LABELING LIST OF DEFICIENCIES

None

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section

Model Labeling	The tablet inactive ingredients are microcrystalline cellulose, low-substituted hydroxypropylcellulose, crospovidone, magnesium stearate (vegetable origin), talc, and colloidal silicon dioxide. The film-coat inactive ingredients are hypromellose, titanium dioxide (E 171), Macrogl 4000, talc, and iron oxide red (E 172). The film-coat for the 24 mg of sacubitril and 26 mg of valsartan tablet and the 97 mg of sacubitril and 103 mg of valsartan tablet also contains iron oxide black (E 172). The film-coat for the 49 mg of sacubitril and 51 mg of valsartan tablet contains iron oxide yellow (E 172).
Previous ANDA Labeling	The tablet inactive ingredients are colloidal silicon dioxide, crospovidone, croscarmellose sodium, magnesium stearate, microcrystalline cellulose and talc. The film-coat inactive ingredients are hypromellose, titanium dioxide, macrogl, talc and iron oxide red. The film-coat for the 24 mg of sacubitril and 26 mg of valsartan tablet and 97 mg of sacubitril and 103 mg of valsartan tablet also contains iron oxide black. The film-coat for the 49 mg of sacubitril and 51 mg of valsartan tablet also contains iron oxide yellow.
Current ANDA Labeling	The tablet inactive ingredients are colloidal silicon dioxide, crospovidone, croscarmellose sodium, magnesium stearate, microcrystalline cellulose and talc. The film-coat inactive ingredients are hypromellose, titanium dioxide, macrogl, talc and iron oxide red. The film-coat for the 24 mg of sacubitril and 26 mg of valsartan tablet and 97 mg of sacubitril and 103 mg of valsartan tablet also contains iron oxide black. The film-coat for the 49 mg of sacubitril and 51 mg of valsartan tablet also contains iron oxide yellow. <u>Reviewers Assessment:</u> Acceptable: No changes noted.

5.1.3 HOW SUPPLIED/STORAGE AND HANDLING (C4)

Table 8: Comparison of Model Labeling to ANDA Labeling

Model Labeling	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. All strengths are packaged in bottles as described below. <table><tr><th>Tablet</th><th>Color</th><th>Debossment</th><th colspan="2">NDC # 0078-XXXX-XX</th></tr><tr><td>Sacubitril/Valsartan</td><td></td><td>“NVR” and</td><td>Bottle of 60</td><td>Bottle of 180</td></tr><tr><td>24 mg/26 mg</td><td>Violet white</td><td>LZ</td><td>0659-20</td><td>0659-67</td></tr><tr><td>49 mg/51 mg</td><td>Pale yellow</td><td>L1</td><td>0777-20</td><td>0777-67</td></tr><tr><td>97 mg/103 mg</td><td>Light pink</td><td>L11</td><td>0696-20</td><td>0696-67</td></tr></table> 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.	Tablet	Color	Debossment	NDC # 0078-XXXX-XX		Sacubitril/Valsartan		“NVR” and	Bottle of 60	Bottle of 180	24 mg/26 mg	Violet white	LZ	0659-20	0659-67	49 mg/51 mg	Pale yellow	L1	0777-20	0777-67	97 mg/103 mg	Light pink	L11	0696-20	0696-67
Tablet	Color	Debossment	NDC # 0078-XXXX-XX																							
Sacubitril/Valsartan		“NVR” and	Bottle of 60	Bottle of 180																						
24 mg/26 mg	Violet white	LZ	0659-20	0659-67																						
49 mg/51 mg	Pale yellow	L1	0777-20	0777-67																						
97 mg/103 mg	Light pink	L11	0696-20	0696-67																						
Previous ANDA Labeling	Sacubitril/valsartan tablets are available as unscored, oval shaped, 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. All strengths are packaged in bottles as described below.																									

Table 8: Comparison of Model Labeling to ANDA Labeling

	Tablet	Color	Debossment	NDC # 69539-XXX-XX	
	Sacubitril/Valsartan		"M" and	Bottle of 60	Bottle of 180
	24 mg/26 mg	Purple	S1	166-60	166-18
	49 mg/51 mg	Light yellow	S2	167-60	167-18
	97 mg/103 mg	Light pink	S3	168-60	168-18
	Store at 25°C (77°F), excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from moisture.				
Current ANDA Labeling	Sacubitril/valsartan tablets are available as unscored, oval shaped, 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. All strengths are packaged in bottles as described below.				
	Tablet	Color	Debossment	NDC # 69539-XXX-XX	
	Sacubitril/Valsartan		"M" and	Bottle of 60	Bottle of 180
	24 mg/26 mg	Purple	S1	166-60	166-18
	49 mg/51 mg	Light yellow	S2	167-60	167-18
	97 mg/103 mg	Light pink	S3	168-60	168-18
	Store at 25°C (77°F), excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from moisture.				
	Reviewers Assessment:				
	Acceptable: No changes noted. We do note that the RLD has a slightly different storage temperature. (b)(4)				
	(b)(4)				

5.1.4 MANUFACTURER, DISTRIBUTOR, AND/OR PACKER (C4)

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements

Previous ANDA Labeling	
Name and Address on ANDA Prescribing Information	Manufactured by: MSN Laboratories Private Limited Telangana – 509 228, INDIA Distributed by: MSN Pharmaceuticals Inc. Piscataway, NJ 08854 -3714 Issued on: 03/2021
Current ANDA Labeling	
Name and Address on	Manufactured by:

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements

ANDA Prescribing Information	MSN Laboratories Private Limited Telangana – 509 228, INDIA Distributed by: MSN Pharmaceuticals Inc. Piscataway, NJ 08854 -3714 Issued on: 12/2021 Reviewers Assessment: Acceptable: No changes noted.
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Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements

Manufactured by	Manufactured for	Distributed by	Distributed for
-----------------	------------------	----------------	-----------------

5.2 CONTAINER LABEL (FOR BLISTERS GO TO UNIT-DOSE BLISTERS) (C4)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Container meets the too small exemption [21CFR 201.10(i)]. Please enter Reviewer/Deficiency Comments if you select Deficiency.
ESTABLISHED/PROPRIETARY NAME and STRENGTH:		
☐	☒	Tall Man lettering complies with recommendations found on FDA webpage .
☐	☒	Established/proprietary name and strength are the most prominent information on the Principal Display Panel.
☐	☒	No intervening text (written, printed, or graphic matter) between established name and strength.
THE FOLLOWING COMPONENTS ARE PROPERLY DISPLAYED:		
☐	☒	Net quantity statement. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Dosage statement.
☐	☒	NDC number : prominence, linear bar code, and its orientation.
☐	☒	Expiration date and lot number (or placeholder).
☐	☒	Equivalency statement (product strength).
☐	☒	Medication Guide Pharmacist instructions [21 CFR 208.24(d)].
☐	☒	Controlled Substance Symbol .
☐	☒	Image of drug product represents the true size, color, and imprint.
☐	☒	Yellow #5 (tartrazine) warning statement is properly displayed.
☐	☒	Alcohol is properly listed [21 CFR 201.10(d)(2)].
☐	☒	Latex warning statement is properly displayed [21 CFR 801.437].
PRODUCT DIFFERENTIATION:		
☐	☒	ANDA is the same color as the RLD labels as required (e.g. warfarin, levothyroxine, enoxaparin). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Multiple strengths are differentiated by use of different color or other acceptable means.
☐	☒	Labels of proposed product is differentiated from related products .
STORAGE, DISPENSING, MANUFACTURER, and PACKAGING:		
☐	☒	Storage/dispensing statement is consistent with the How Supplied section of the insert/RLD/USP. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Manufacturer/Distributor/Packager statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].

Deficiency	No Deficiency	
☐	☒	Tamper evident (controlled substances) requirements are met.
☐	☒	Use of child-resistant closure (CRC) or non-CRC is appropriate. Describe container closure , cite source, and any issues in Reviewer Comments below. Please enter Reviewer/Deficiency Comments if you select Deficiency.
OVERALL ASSESSMENT:		
☐	☒	Requirements met for the required label statements (21 CFR 201.15 and 21 CFR 201.100). Please enter Reviewer/Deficiency Comments if you select Deficiency.
Reviewer Comments: The 10/30/2019 container labels were determined adequate. Those labels will be attached to this review for completeness.		
Deficiency Comments:		

5.3 PRESCRIBING INFORMATION (C4)

Reviewer Assessment:

Deficiency	No Deficiency	
HIGHLIGHTS:		
☐	☒	Contact information for applicant and FDA are listed correctly.
☐	☒	Revision date appears at end of HIGHLIGHTS section.
DESCRIPTION/INACTIVE INGREDIENTS:		
☐	☒	Appropriate warning/precaution statements for inactive ingredients are present (21 CFR 201) Check only if applicable: ☒ Sulfite (21 CFR 201.22) ☐ Yellow #5 (Tartrazine) (21 CFR 201.20) ☐ Phenylalanine/aspartame (21 CFR 201.21) ☐ Latex (21 CFR 801.437). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Alcohol is properly listed [21 CFR 201.10(d)(2)].
☐	☒	Gluten statement is appropriately stated. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Sterile product statement [21 CFR 201.57(c)(12)(D)].
☐	☒	Dosage form and route of administration properly listed [21 CFR 201.57(c)(12)(B)].
HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:		
☐	☒	All submitted labels and labeling are consistent with the HOW SUPPLIED section.
☐	☒	Physical description (e.g. scoring, color, imprint, capsule size, nozzle tip, cap color) of the finished product in the HOW SUPPLIED section are appropriately displayed.
☐	☒	NDC numbers are present.
☐	☒	Drug product is the same color as the RLD's drug product as required (e.g. warfarin, levothyroxine, enoxaparin).
☐	☒	Storage or dispensing statement is acceptable compared to the RLD/USP monograph. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	"Discard unused portion" for single-dose products.
☐	☒	Manufacturer/Distributor/Packager statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:		
☐	☒	STIC requirements addressed appropriately.
☐	☒	Intent to join the Antiretroviral Pregnancy Registry (APR) upon full approval.
☐	☒	Pregnancy registry information is appropriately included/excluded as required for the RLD. Please

Deficiency	No Deficiency	
		enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Patent/exclusivity carve out is acceptable. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☒	☐	Prescribing Information is the same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8) . Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

(b)(4)

Deficiency Comments:

Deficiency # 1

Created in C4

Prescribing Information

Response / Assessment:

HIGHLIGHTS:

i. Indications and Usage: Revise to read, "to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure and reduced ejection fraction (1.1).".

(b)(4)

Deficiency # 2

Created in C4

Prescribing Information

Response / Assessment:

INDICATIONS AND USAGE:

i. Revise to read, "Sacubitril and valsartan is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure and reduced ejection fraction."
ii. Retain the sentence, "LVEF is a variable measure, so use clinical judgment in deciding whom to treat [*see Clinical Studies (14.1)*].".

Deficiency # 3

Created in C4

Prescribing Information

Response / Assessment:

(b)(4)

Deficiency # 4

Created in C4

Prescribing Information

Response / Assessment:

(b)(4)

5.4 OTHER PATIENT LABELING (C4)

Reviewer Assessment:

Deficiency	No Deficiency	
☒	☐	Other patient labeling is the same as the model labeling except for allowable differences. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:**Deficiency Comments:**

Deficiency # 1

Created in C4

Patient Information Leaflet

Response / Assessment:

At the end of the list of inactive ingredients, include, "Prepared sacubitril and valsartan oral suspension also contains Ora-Sweet SF® and Ora-Plus.®". Additionally, include the disclaimer, "All brand names listed are the registered trademarks of their respective owners. ".

6 COMMENTS/CONSULTS FOR OTHER DISCIPLINES (C4)

A labeling statement required verification from another division discipline. Check only if applicable.

Reviewer Assessment:

☐	Rubber
☐	Latex
☐	Gluten
☐	Alcohol (ethanol)
☐	Aluminum (small/large volume parenteral and pharmacy bulk package)
☐	Sulfite
☐	Phenylalanine (aspartame) - content calculation
☐	Yellow #5 (tartrazine)
☐	Ghost tablet/capsule (i.e. solid or semi-solid mass in stool)
☐	Other

Describe questions/issue(s) sent to and/or received from other discipline(s) (e.g., OPQ, OB): (For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue)

Reviewer Comments:

(b)(4)

Deficiency Comments:



Wan
Lee

Digitally signed by Wan Lee
Date: 4/26/2022 03:52:23PM
GUID: 582a2cfa001b51dba58dfaf180bcd09a



Betty
Turner

Digitally signed by Betty Turner
Date: 4/27/2022 08:42:08AM
GUID: 508da70600028acef381be737f7836a9

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations

Office of Generic Drugs (OGD)

Center for Drug Evaluation and Research (CDER)

Date of This Review	April 19, 2021
ANDA Number(s)	213748
Review Number	3
Applicant Name	MSN Laboratories Private Limited
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Sacubitril and Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg
Proposed Proprietary Name	NA
Submission Received Date	March 17, 2021 (Labeling Amendment – RLD Update)
Primary Labeling Reviewer	Wan Lee, PharmD
Secondary Labeling Reviewer	Refer to signature page
Review Conclusion ☐ ACCEPTABLE – No Comments ☐ ACCEPTABLE – Include Post Approval Comments ☒ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for Letter to Applicant ☐ Major Deficiency[†] – Refer to Labeling Deficiencies and Comments for Letter to Applicant [†]Theme - Choose an item. Justification for Major Deficiency - Choose an item. *Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.	
On Policy Alert List ☒ Yes ☐ No Combined Insert/Outsert ☐ Yes ☒ No (If yes, indicate ANDA number)	

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling deficiencies based on your submission received March 17, 2021:

GENERAL COMMENT

(b)(4)

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission (s) received (add date)

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.3 POST APPROVAL REVISIONS

These comments will be addressed post approval (in the first labeling supplement review).
Click here to enter text.

2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment to firm's response as well as any new deficiencies found in this cycle. Include the previous review cycle and the review's submission date(s) [e.g. "The below comments are from the labeling review C3 based on the submission dated 7/4/15"].

Reviewer Comments:

Regulatory History

A Major CR was issued on 6/8/2020 with deficiencies in Quality, Biopharmaceutics, and Facility.

OTHER DISCIPLINE REVIEWS

3/10/2021 Biopharmaceutics Assessment – Adequate

3/16/2021 Drug Quality Recommendation – CR – Minor

Submission(s) Assessed	Document Date	Discipline(s) Affected
CR 01	8/19/2020	Quality
Amendment-Response to DRL	2/27/2020	Quality
Original	7/8/2019	All
Labeling-Response to Discipline Review Letter*	10/30/2019	Labeling

*Preparation of oral suspension added in label to be in line with RLD, but no supporting quality information provided

1.14 Labeling

Labeling & Prescribing Information

DESCRIPTION (Rx insert or Active Ingredient(s), and Inactive Ingredients in DRUG FACTS for OTC):

Is the information accurate? ☒ Yes ☐ No

If "No," explain.

Is the drug product subject of a USP monograph? ☐ Yes ☒ No

If "Yes," does labeling have accurate USP statement in the DESCRIPTION (for Rx) or Other Information section of DRUG FACTS (for OTC)?

☐ Yes ☐ No ☐ Statement not needed

If NO, what is/are the needed statement(s)? _____

HOW SUPPLIED section (Rx insert) or Storage (in DRUG FACTS for OTC)

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Is tamper evident feature provided in the container/closure for the OTC products or Controlled Substance (CII – CIV) products? ☐ Yes ☐ No
☒ N/A (NOT OTC or Controlled Substance)

If "No," explain.

For solid oral drug products, only: drug product length(s) of commercial batch(es):

ANDA Strength	Length (MM)	Imprint Code
24 mg/ 26 mg	10.00 x 4.00	one side debossed with 'M' and other side debossed with 'S1'
49 mg/ 51 mg	13.00 x 5.10	one side debossed with 'M' and other side debossed with 'S2'
97 mg/ 103 mg	15.00 x 5.90	one side debossed with 'M' and other side debossed with 'S3'

Send issue to the Labeling assessor through the Platform with a list of quality-related labeling deficiencies and also record reference number or link for all the issues:

Issue Description	Issue Reference Number or Link

LABELING LIST OF DEFICIENCIES

None

3/16/2021 Facilities Assessment – Inadequate - Minor

List Submissions being assessed (Table):

Document Description (SD #)	Date Received
Original Submission, Seq. 0000 (1)	07/08/2019
CMC Amendment (Response to DRL), Seq. 0005 (6)	02/27/2020
CMC Amendment (Response to CRL), Seq. 0007 (8); Amend-8	08/19/2020
CMC Amendment (Response to IR), Seq. 0008 (9)	08/28/2020

Note: Seq. 0001 (2), 0002 (3), 0003 (4), 0004 (5), and 0006 (7) are not CMC related submissions.

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review?
NO

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Reviewer Comments:

The container labels from the October 30, 2019 submission were determined acceptable. Those labels will be attached to this review for completeness.

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s) [e.g. resolution of any pending chemistry review or issue].

Reviewer Comments:**Drug Facts**

(b)(4)

In this amendment, the Applicant provided revised labeling in accordance to the BPCA carve-out template.

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT**3.1 REGULATORY INFORMATION**

Are there any pending issues in [DLR's SharePoint Drug Facts](#)? YES

If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review

Is the drug product listed in the Policy Alert Tracker on [OGD's SharePoint](#)? YES

If Yes, please explain.

CP	FDA-2019-P-1893	Entresto	sacubitril/ valsartan tablets	Revises FDA's Draft Guidance document regarding sacubitril/valsartan oral tablets to recommend that API sameness be established by showing that the chemical structure of each active ingredient in the finished dosage form of a proposed generic is identical to the chemical structure of each active ingredient in the RLD, including all ionic bonds; (3) Further revise the Draft Guidance to include BE and PK requirements.	207620
No Approval Actions (TA/AP) can be taken prior to contacting Policy Lead		All disciplines can continue communications (CRL, IR/DRL); CC should contact Policy if related to CP		4/19/2019	Lauren Clurca

Is the drug product listed on the [Susceptibility Test Interpretive Criteria web page](#)? NO

3.2 MODEL LABELING

Table 1: Review Model Labeling
(Check the box used as the Model Labeling)

☒ **MOST RECENTLY APPROVED NDA MODEL LABELING**

(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so enter the most recently approved ANDA labeling information as applicable.)

NDA# /Supplement# (S-000 if original): 207620/S-018

Supplement Approval Date: 2/16/2021

Proprietary Name: Entresto

Established Name: Sacubitril and Valsartan Tablets

Description of Supplement:

This Prior Approval supplemental new drug application 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.

2/16/2021 RPM Review

Proposed Indication in original supplemental submission: to reduce worsening heart failure (total heart failure hospitalizations and urgent heart failure visits) in patients with chronic heart failure and preserved ejection fraction

Amended Proposed Indication in original submission: to reduce worsening heart failure (total heart failure hospitalizations and urgent heart failure visits) in patients with chronic heart failure and preserved ejection fraction **with left ventricular ejection fraction (LVEF) below normal**

Final indication: 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.

LVEF is a variable measure, so use clinical judgment in deciding whom to treat

Entresto was also being studied in patients with preserved ejection fraction (HFpEF). The pivotal trial known as **PARAGON-HF** was a double-blind randomized clinical trial comparing Entresto 200 mg BID to Valsartan 160 mg BID. Eligible patients had symptomatic HFpEF (NYHA class II-IV) with LVEF $\geq$ 45% requiring diuretics. Other entry criteria were left ventricular hypertrophy (LVH) or left atrial enlargement (LAE), and elevated N-terminal-proB-type natriuretic peptide (NT-proBNP). The primary efficacy endpoint was a composite of total (first and recurrent) hospitalizations for heart failure and cardiovascular death. Secondary endpoints were NYHA class, KCCQ, renal composite outcome and all-cause mortality. The trial fell short of meeting statistical significance, but the Division suggested that the data might support a new claim. **This supplement was submitted proposing a new indication to include HFpEF patients.**

☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING**

ANDA#/Supplement# (S-000 if original): Click here to enter text.

Supplement Approval Date: Click here to enter text.

Proprietary Name: Click here to enter text.

Established Name: Click here to enter text.

Description of Supplement:

Table 1: Review Model Labeling
(Check the box used as the Model Labeling)

☒ **TEMPLATE** (e.g., BPCA, PREA, Carve-out):

(b)(4)

☐ **OTHER (Describe):** Click here to enter text.

Reviewer Assessment:

Is the Prescribing Information or Drug Facts Labeling (OTC) same as the model labeling, except for differences allowed under [21 CFR 314.94\(a\)\(8\)](#)? **NO**

Are the specific requirements for format met under [21 CFR 201.57\(new\)](#) or [201.80\(old\)](#), or [201.66 \(OTC\)](#)? **YES**

Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

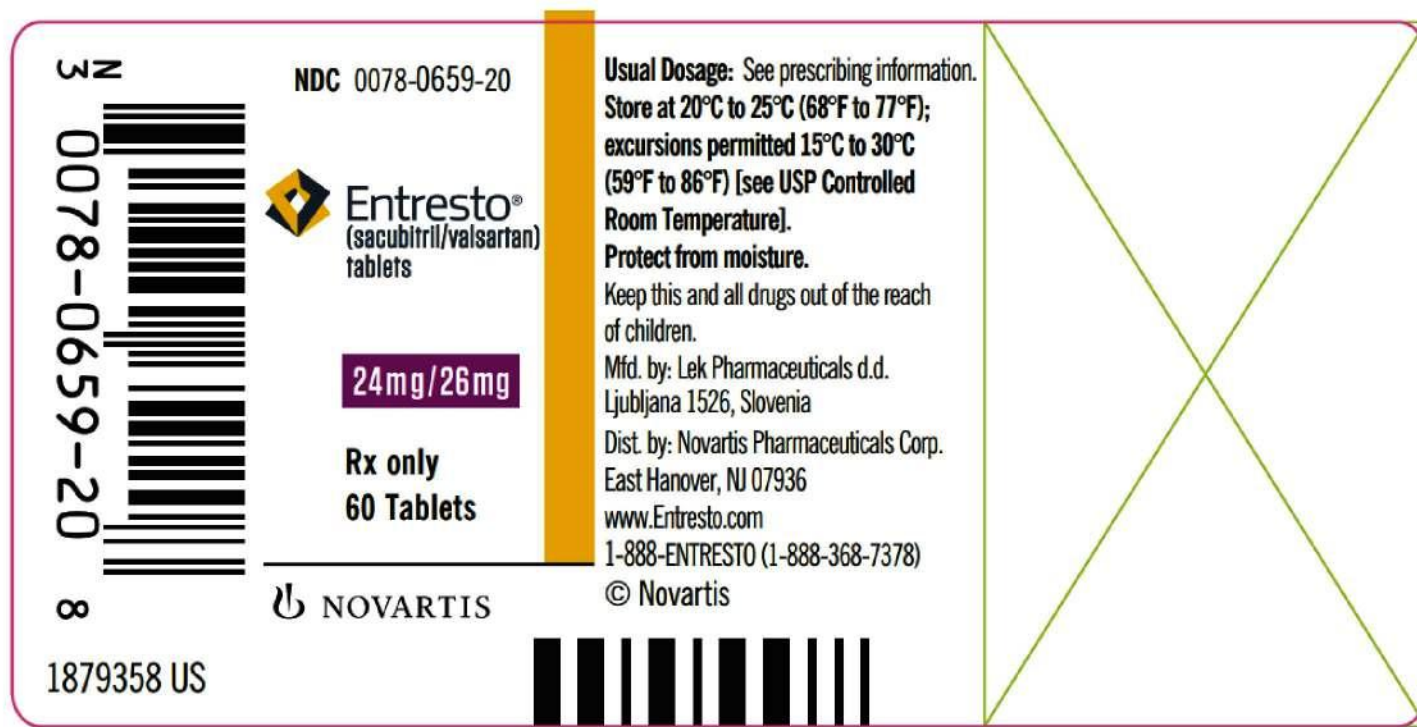
Reviewer Comments:

-
-

(b)(4)

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: DARRTS; SUPP-017 approved on 9/10/2020]



3 N



3

1879360 US

NDC 0078-0659-67



Entresto®
(sacubitril/valsartan)
tablets

24 mg/26 mg

Rx only
180 Tablets

NOVARTIS

Usual Dosage: See prescribing information.
Store at 20°C to 25°C (68°F to 77°F);
excursions permitted 15°C to 30°C
(59°F to 86°F) [see USP Controlled
Room Temperature].
Protect from moisture.

Keep this and all drugs out of the reach
of children.

Mfd. by: Lek Pharmaceuticals d.d.
Ljubljana 1526, Slovenia

Dist. by: Novartis Pharmaceuticals Corp.
East Hanover, NJ 07936

www.Entresto.com

1-888-ENTRESTO (1-888-368-7378)

© Novartis



3 N



9

1879776 US

NDC 0078-0777-20



Entresto®
(sacubitril/valsartan)
tablets

49 mg/51 mg

Rx only
60 Tablets

NOVARTIS

Usual Dosage: See prescribing information.
Store at 20°C to 25°C (68°F to 77°F);
excursions permitted 15°C to 30°C
(59°F to 86°F) [see USP Controlled
Room Temperature].
Protect from moisture.

Keep this and all drugs out of the reach
of children.

Mfd. by: Lek Pharmaceuticals d.d.
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Dist. by: Novartis Pharmaceuticals Corp.
East Hanover, NJ 07936

www.Entresto.com

1-888-ENTRESTO (1-888-368-7378)

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3 N



4

1879793 US

NDC 0078-0777-67



Entresto®
(sacubitril/valsartan)
tablets

49mg/51mg

Rx only
180 Tablets



NOVARTIS

Usual Dosage: See prescribing information.

Store at 20°C to 25°C (68°F to 77°F); excursions permitted 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Protect from moisture.

Keep this and all drugs out of the reach of children.

Mfd. by: Lek Pharmaceuticals d.d.
Ljubljana 1526, Slovenia

Dist. by: Novartis Pharmaceuticals Corp.
East Hanover, NJ 07936

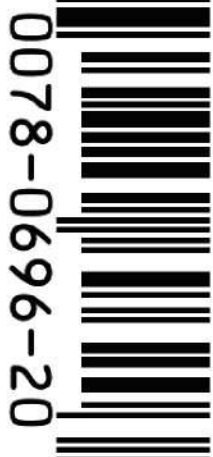
www.Entresto.com

1-888-ENTRESTO (1-888-368-7378)

© Novartis



3 N



3

1879824 US

NDC 0078-0696-20



Entresto®
(sacubitril/valsartan)
tablets

97mg/103mg

Rx only
60 Tablets



NOVARTIS

Usual Dosage: See prescribing information.

Store at 20°C to 25°C (68°F to 77°F); excursions permitted 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Protect from moisture.

Keep this and all drugs out of the reach of children.

Mfd. by: Lek Pharmaceuticals d.d.
Ljubljana 1526, Slovenia

Dist. by: Novartis Pharmaceuticals Corp.
East Hanover, NJ 07936

www.Entresto.com

1-888-ENTRESTO (1-888-368-7378)

© Novartis



3 N

0078-0696-67

8



Entresto®
(sacubitril/valsartan)
tablets

97 mg / 103 mg

Rx only
180 Tablets

NDC 0078-0696-67

Usual Dosage:
See prescribing information.

Store at 20°C to 25°C (68°F to 77°F);
excursions permitted 15°C to 30°C
(59°F to 86°F) [see USP Controlled
Room Temperature].
Protect from moisture.

Keep this and all drugs out of the reach
of children.

Mfd. by: Lek Pharmaceuticals d.d.
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East Hanover, NJ 07936

www.Entresto.com
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1879829 US

NOVARTIS



3.4 UNITED STATES PHARMACOPEIA (USP)

The [USP](#) was searched on 4/19/2021.

Table 2: United States Pharmacopeia (USP)

	YES or NO	Date	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
Currently Official	NO		NA	NA
Not Yet Official	NO	NA	NA	NA

Reviewer Assessment:

Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labeling and labels? **NA**

Reviewer Comments:

None

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 4/19/2021.

Table 3 provides Orange Book patents for the Model Labeling NDA 207620 and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling

Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter Carve-out or None)
7468390	11/27/2023			IV	3/23/20	None
7468390*PED	05/27/2024					
8101659	01/14/2023			IV	3/23/20	None

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
8101659*PED	07/14/2023					
8404744	01/14/2023			IV	3/23/20	None
8404744*PED	07/14/2023					
8796331	01/14/2023	U-1723	TREATMENT OF HEART FAILURE	IV	3/23/20	None
8796331*PED	07/14/2023					
8877938	05/27/2027			IV	3/23/20	None
8877938*PED	11/27/2027					
9388134	11/08/2026	U-1723	TREATMENT OF HEART FAILURE	IV	3/23/20	None
9388134*PED	05/08/2027					
9517226	08/22/2033	U-3084	TREATMENT OF HEART FAILURE WITH PRESERVED EJECTION FRACTION	Need to address		
9937143	08/22/2033	U-3084	TREATMENT OF HEART FAILURE WITH PRESERVED EJECTION FRACTION	Need to address		

Reviewer Assessment:

Is the applicant's "patent carve out" acceptable? **NA**

Reviewer Comments:

(b)(4)

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact (enter Carve-out or None)
NCE *PED*	01/07/2021	NEW CHEMICAL ENTITY	MSN Laboratories Private Ltd commits not to market this product until the expiration of NCE*PED exclusivity.	3/23/2020	None
NPP	10/01/2022	NEW PATIENT POPULATION	With respect to the exclusivity code "NPP *PED" expiring on April 01, 2023. The proposed labeling for the MSN product does not include information associated with the NPP*PED exclusivity.	3/23/2020	Carve-out
NPP *PED	04/01/2023	PEDIATRIC EXCLUSIVITY			
M-82	02/16/2024	LABELING REVISIONS RELATED TO CLINICAL STUDIES	Need to address		

* Expired

Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **YES**

Reviewer Comments:

•

(b)(4)

DELETED PAGES INFORMATION SHEET

IT IS NOT REASONABLE TO SEGREGATE MEANINGFUL PORTIONS OF THE RECORD FOR RELEASE.

INFORMATION HAS BEEN WITHHELD IN ITS ENTIRETY IN ACCORDANCE WITH THE FOLLOWING EXEMPTIONS(S):

(b) (4)

5 U.S.C. 552 (b) (4) - trade secrets and commercial or financial information obtained from a person and privileged or confidential.

(b)(4)

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the inactive ingredients, dosage form description, package sizes, and manufacturer/distributor/packer statements of the Prescribing Information or Drug Facts for OTC products when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or Inactive Ingredients (OTC)? **NO**
Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **NO**
Are there changes to the manufacturer/distributor/packer statements? **NO**
If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)

Previous Labeling Review	Currently Proposed	Assessment
The tablet inactive ingredients are colloidal silicon dioxide, crospovidone, croscarmellose sodium, magnesium stearate, microcrystalline cellulose and talc. The film-coat inactive ingredients are hypromellose, titanium dioxide, macrogol, talc and iron oxide red. The film-coat for the 24 mg of sacubitril and 26 mg of valsartan tablet and 97 mg of sacubitril and 103 mg of valsartan tablet also contains iron oxide black. The film-coat for the 49 mg of sacubitril and 51 mg of valsartan tablet also contains iron oxide yellow.	The tablet inactive ingredients are colloidal silicon dioxide, crospovidone, croscarmellose sodium, magnesium stearate, microcrystalline cellulose and talc. The film-coat inactive ingredients are hypromellose, titanium dioxide, macrogol, talc and iron oxide red. The film-coat for the 24 mg of sacubitril and 26 mg of valsartan tablet and 97 mg of sacubitril and 103 mg of valsartan tablet also contains iron oxide black. The film-coat for the 49 mg of sacubitril and 51 mg of valsartan tablet also contains iron oxide yellow.	Acceptable: No changes noted.

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products

Previous Labeling Review					Currently Proposed					Assessment
Sacubitril/valsartan tablets are available as unscored, oval shaped, 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. All strengths are packaged in bottles as described below.					Sacubitril/valsartan tablets are available as unscored, oval shaped, 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. All strengths are packaged in bottles as described below.					Acceptable: No changes noted.
Tablet	Color	Debossment	NDC # 69539-XXX-XX		Tablet	Color	Debossment	NDC # 69539-XXX-XX		
Sacubitril/Valsartan		"M" and	Bottle of 60	Bottle of 180	Sacubitril/Valsartan		"M" and	Bottle of 60	Bottle of 180	
24 mg/26 mg	Purple	S1	166-60	166-18	24 mg/26 mg	Purple	S1	166-60	166-18	
49 mg/51 mg	Light yellow	S2	167-60	167-18	49 mg/51 mg	Light yellow	S2	167-60	167-18	
97 mg/103 mg	Light pink	S3	168-60	168-18	97 mg/103 mg	Light pink	S3	168-60	168-18	
Store at 25°C (77°F), excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from moisture.					Store at 25°C (77°F), excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from moisture.					

Table 7: Manufacturer/Distributor/Packer Statements

Previous Labeling Review	Currently Proposed	Assessment
Manufactured by: MSN Laboratories Private Limited Telangana – 509 228, INDIA Distributed by: MSN Pharmaceuticals Inc. Piscataway, NJ 08854 -3714	Manufactured by: MSN Laboratories Private Limited Telangana – 509 228, INDIA Distributed by: MSN Pharmaceuticals Inc. Piscataway, NJ 08854 -3714	Acceptable: No changes noted.

5. COMMENTS/CONSULTS FOR OTHER DISCIPLINES

Describe questions, issues and consults sent to and/or received from other discipline(s) (e.g., OPQ, OB, DCR):

Refer to the [Consult Screening flow chart](#) to determine any necessary consults.

(For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue). Reminder: Refer to chemistry review to verify labeling section (per Chemistry-Labeling MOU) is complete. Refer to DCR review for combination product to verify if labeling comments were communicated to applicant.

Reviewer Comments:

None

6. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for all labeling pieces for this application.

For each row, you **MUST** choose an item “Final, Draft, or “NA”. If you enter “NA” under the second column, you do NOT need to enter “NA” for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	Packaging Sizes	Submission Received Date	Recommendation
Container	Final	24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg (60s and 180s count bottles)	10/30/2019	Satisfactory
Blister	NA			
Carton	NA			
(Other – specify)	NA			
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	Revision Date and/or Code	Submission Received Date	Recommendation
Prescribing Information	Draft	3/2021	3/17/2021	Revise
Medication Guide	NA			
Patient Information	Draft	3/2021	3/17/2021	Revise



Wan
Lee

Digitally signed by Wan Lee

Date: 4/19/2021 01:43:59PM

GUID: 582a2cfa001b51dba58dfaf180bcd09a



Betty
Turner

Digitally signed by Betty Turner

Date: 4/19/2021 05:05:45PM

GUID: 508da70600028acef381be737f7836a9

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations

Office of Generic Drugs (OGD)

Center for Drug Evaluation and Research (CDER)

Date of This Review	April 9, 2020
ANDA Number(s)	213748
Review Number	2
Applicant Name	MSN Laboratories Private Limited
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Sacubitril and Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg
Proposed Proprietary Name	None
Submission Received Date	March 3, 2020 (Revised labeling BPCA template) October 30, 2019 (Response to Labeling DRL)
Primary Labeling Reviewer	Wan Lee, PharmD
Secondary Labeling Reviewer	Refer to signature page
Review Conclusion ☒ ACCEPTABLE – No Comments ☐ ACCEPTABLE – Include Post Approval Comments ☐ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for Letter to Applicant ☐ Major Deficiency [†] – Refer to Labeling Deficiencies and Comments for Letter to Applicant [†] Theme - Choose an item. Justification for Major Deficiency - Choose an item. *Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.	
On Policy Alert List	☒ Yes ☐ No
Combined Insert/Outsert	☐ Yes ☒ No (If yes, indicate ANDA number)

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on (add date) based on your submission(s) received (add date):

1. GENERAL COMMENTS

Comment

2. CONTAINER LABEL

a. Comment

b. Comment

3. CARTON LABELING

4. PRESCRIBING INFORMATION

a. Comment

b. Subheading

i. Comment

ii. Comment

5. MEDICATION GUIDE

6. STRUCTURED PRODUCT LABELING (SPL)

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with [Choose an item](#), all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submissions received October 30, 2019 and March 3, 2020.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.3 POST APPROVAL REVISIONS

These comments will be addressed post approval (in the first labeling supplement review).
Click here to enter text.

2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment to firm's response as well as any new deficiencies found in this cycle. Include the previous review cycle and the review's submission date(s) [e.g. "The below comments are from the labeling review C3 based on the submission dated 7/4/15"].

Reviewer Comments:

The below comments are from the labeling review C1 based on the submission dated July 8, 2019.

1. GENERAL COMMENTS

(b)(4)

2. CONTAINER LABEL

- a. We note that the RLD does not contain a Medication Guide but rather a Patient Information leaflet. We also note that in your submission, you have provided a similar document.

(b)(4)

- b. Revise the "(b)(4)" statement to read "Each film-coated tablet contains XX mg of sacubitril and XX mg of valsartan." (b)(4)
- c. We recommend revising your storage statement to read, "Store at 25°C (77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from moisture." (note revise "to" to "between").

Response:

We acknowledge the reviewer comments (2.a, 2.b and 2.c). In accordance to the reviewer's recommendations, we have revised container labels. The revised container labels and annotated

Reviewer Comments:

This is acceptable and this is consistent with their PI.

3. PRESCRIBING INFORMATION

- a. There should not be white space between "HIGHLIGHTS OF PRESCRIBING INFORMATION" and the Highlights statement.
- b. HIGHLIGHTS and FULL PRESCRIBING INFORMATION: In the boxed warning, revise "(b)(4)" to the drug product, "sacubitril and valsartan tablets".
- c. (b)(4)
- d. DOSAGE FORMS AND STRENGTHS: To align with the RLD, we recommend including "unscored" as a characteristic of the drug product.
- e. USE IN SPECIFIC POPULATIONS, Lactation: In the last sentence of the "Data" subsection, ensure there is a space between "of valsartan".
- f. HOW SUPPLIED:
- i. To align with the RLD, we recommend including "unscored" as a characteristic of the drug product.

- ii. We recommend revising your storage statement to read, “Store at 25°C (77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]”. Retain all other information.

Response:

We acknowledge the reviewer comment. In accordance to the reviewer’s recommendations [3.a, 3.b, 3.c, 3.d, 3.e and 3.f (i, ii)] Prescribing Information has been updated.

Reviewer Comments:

This is acceptable.

4. PATIENT INFORMATION

- a. We recommend revising your established name to “Sacubitril and Valsartan Tablets” to be consistent throughout your labeling.
- b. Revise your proposed pronunciation of the non-proprietary name to conform to the phonetic pronunciation in the current USP Dictionary of USAN and International Drug Names (sak ue’ bi tril and val sar’ tan).
- c. To separate each section, we recommend using boxes or white space for easy readability. Please refer to RLD.

d.

(b)(4)

Response:

We acknowledge the reviewer comment. In accordance to the reviewer’s recommendations (4.a, 4.b, 4.c and 4.d Patient information is updated.

Reviewer Comments:

This is acceptable.

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review?
NO

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Reviewer Comments:

None

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s) [e.g. resolution of any pending chemistry review or issue].

Reviewer Comments:**Drug Facts:**

(b)(4)

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT**3.1 REGULATORY INFORMATION**

Are there any pending issues in [DLR's SharePoint Drug Facts](#)? YES

If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review

Is the drug product listed in the Policy Alert Tracker on [OGD's SharePoint](#)? YES

If Yes, please explain.

				Requests FDA to: (1) Require ANDAs that reference ENTRESTO to demonstrate API sameness; (2) Revise FDA's Draft Guidance document regarding sacubitril/valsartan oral tablets to recommend that API sameness be established by showing that the chemical structure of each active ingredient in the finished dosage form of a proposed generic is identical to the chemical structure of each active ingredient in the RLD, including all ionic bonds; (3) Further revise the Draft Guidance to include BE and PK requirements.	
CP	FDA-2019-P-1893	Entresto	sacubitril; valsartan tablets		207620
No Approval Actions (AP/TA) can be taken prior to contacting Policy Lead		All disciplines can continue communications (CRL, IR/DRL); CC should contact Policy if related to CP			4/19/2019 Margaret BurnsRath

Is the drug product listed on the [Susceptibility Test Interpretive Criteria web page](#)? NO

3.2 MODEL LABELING

Table 1: Review Model Labeling
(Check the box used as the Model Labeling)

☐ **MOST RECENTLY APPROVED NDA MODEL LABELING**

(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so enter the most recently approved ANDA labeling information as applicable.)

NDA# /Supplement# (S-000 if original): NDA 207620/S-013

Supplement Approval Date: October 1, 2019

Proprietary Name: Entresto

Established Name: sacubitril/valsartan tablets

Description of Supplement:

This Prior Approval supplemental new drug application, submitted in response to a Pediatric Written Request, supports a labeled indication for use of Entresto® for 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.

OTHER IMPORTANT INFORMATION:

Supplement-016 (CMC CBE-30); Approved 2/20/2020:

(b)(4)

☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING**

ANDA#/Supplement# (S-000 if original): Click here to enter text.

Supplement Approval Date: Click here to enter text.

Proprietary Name: Click here to enter text.

Established Name: Click here to enter text.

Description of Supplement:

☒ **TEMPLATE (e.g., BPCA, PREA, Carve-out):**

(b)(4)

☐ **OTHER (Describe):** Click here to enter text.

Reviewer Assessment:

Is the Prescribing Information or Drug Facts Labeling (OTC) same as the model labeling, except for differences allowed under [21 CFR 314.94\(a\)\(8\)](#)? **YES**

Are the specific requirements for format met under [21 CFR 201.57\(new\)](#) or [201.80\(old\)](#), or [201.66 \(OTC\)](#)? **YES**

Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

Reviewer Comments:

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: DARRTS; CMC SUPPL-16; approved 2/20/2020]

24 mg/26 mg tablet Container Labels

1825772 USS	Physician Sample Not for Sale	Entresto® (sacubitril/valsartan) tablets 24 mg/26 mg Rx only 28 Tablets	Usual Dosage: See prescribing information. Store at 20°C to 25°C (68°F to 77°F); excursions permitted 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from moisture. Keep this and all drugs out of the reach of children. Mfd. by: Novartis Singapore Pharmaceutical Manufacturing Pte. Ltd., 637461 Singapore Dist. by: Novartis Pharmaceuticals Corp. East Hanover, NJ 07936 www.Entresto.com 1-888-ENTRESTO (1-888-368-7378) ©Novartis 0078-9659-50
	NOVARTIS		



3 0078-0659-20 8 1826195 US	NDC 0078-0659-20	Entresto® (sacubitril/valsartan) tablets 24 mg/26 mg Rx only 60 Tablets	Usual Dosage: See prescribing information. Store at 20°C to 25°C (68°F to 77°F); excursions permitted 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from moisture. Keep this and all drugs out of the reach of children. Mfd. by: Novartis Singapore Pharmaceutical Manufacturing Pte. Ltd., 637461 Singapore Dist. by: Novartis Pharmaceuticals Corp. East Hanover, NJ 07936 www.Entresto.com 1-888-ENTRESTO (1-888-368-7378) © Novartis
	NOVARTIS		



3 0078-0659-67 3 1826197 US	NDC 0078-0659-67  Entresto® (sacubitril/valsartan) tablets 24 mg/26 mg Rx only 180 Tablets  NOVARTIS	Usual Dosage: See prescribing information. Store at 20°C to 25°C (68°F to 77°F); excursions permitted 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from moisture. Keep this and all drugs out of the reach of children. Mfd. by: Novartis Singapore Pharmaceutical Manufacturing Pte. Ltd., 637461 Singapore Dist. by: Novartis Pharmaceuticals Corp. East Hanover, NJ 07936 www.Entresto.com 1-888-ENTRESTO (1-888-368-7378) © Novartis
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49 mg/51 mg tablet Container Labels

1826194 USS	Physician Sample Not for Sale  Entresto® (sacubitril/valsartan) tablets 49 mg / 51mg Rx only 28 Tablets  NOVARTIS	Usual Dosage: See prescribing information. Store at 20°C to 25°C (68°F to 77°F); excursions permitted 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from moisture. Keep this and all drugs out of the reach of children. Mfd. by: Novartis Singapore Pharmaceutical Manufacturing Pte. Ltd., 637461 Singapore Dist. by: Novartis Pharmaceuticals Corp. East Hanover, NJ 07936 www.Entresto.com 1-888-ENTRESTO (1-888-368-7378) ©Novartis 0078-9777-50
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3 N
0078-0777-20
9
1826198 US



NDC 0078-0777-20



49 mg/51 mg

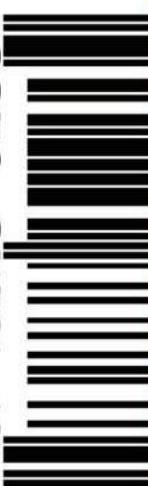
Rx only
60 Tablets



Usual Dosage: See prescribing information.
Store at 20°C to 25°C (68°F to 77°F);
excursions permitted 15°C to 30°C
(59°F to 86°F) [see USP Controlled
Room Temperature].
Protect from moisture.
Keep this and all drugs out of the reach
of children.
Mfd. by: Novartis Singapore Pharmaceutical
Manufacturing Pte. Ltd., 637461 Singapore
Dist. by: Novartis Pharmaceuticals Corp.
East Hanover, NJ 07936
www.Entresto.com
1-888-ENTRESTO (1-888-368-7378)
© Novartis



3 N
0078-0777-67
4
1826200 US



NDC 0078-0777-67



49 mg/51 mg

Rx only
180 Tablets



Usual Dosage: See prescribing information.
Store at 20°C to 25°C (68°F to 77°F);
excursions permitted 15°C to 30°C
(59°F to 86°F) [see USP Controlled
Room Temperature].
Protect from moisture.
Keep this and all drugs out of the reach
of children.
Mfd. by: Novartis Singapore Pharmaceutical
Manufacturing Pte. Ltd., 637461 Singapore
Dist. by: Novartis Pharmaceuticals Corp.
East Hanover, NJ 07936
www.Entresto.com
1-888-ENTRESTO (1-888-368-7378)
© Novartis



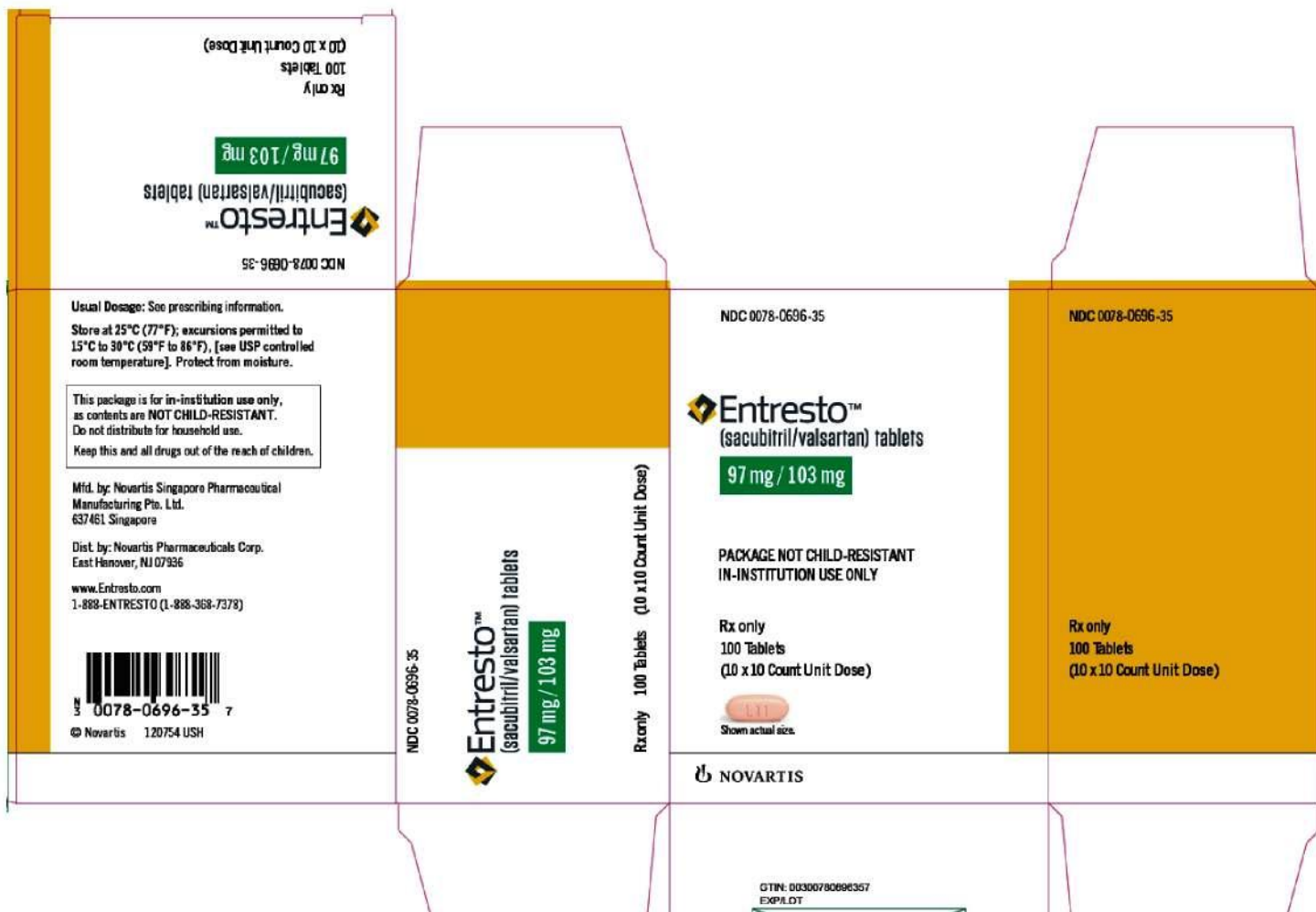
97 mg/103 mg tablet Container Labels

3 N 0078-0696-20 3 1826201 US	NDC 0078-0696-20  Entresto® (sacubitril/valsartan) tablets 97 mg / 103 mg Rx only 60 Tablets  NOVARTIS	Usual Dosage: See prescribing information. Store at 20°C to 25°C (68°F to 77°F); excursions permitted 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from moisture. Keep this and all drugs out of the reach of children. Mfd. by: Novartis Singapore Pharmaceutical Manufacturing Pte. Ltd., 637461 Singapore Dist. by: Novartis Pharmaceuticals Corp. East Hanover, NJ 07936 www.Entresto.com 1-888-ENTRESTO (1-888-368-7378) © Novartis
3 N 0078-0696-67 8 1826202 US	NDC 0078-0696-67  Entresto® (sacubitril/valsartan) tablets 97 mg / 103 mg Rx only 180 Tablets  NOVARTIS	Usual Dosage: See prescribing information. Store at 20°C to 25°C (68°F to 77°F); excursions permitted 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from moisture. Keep this and all drugs out of the reach of children. Mfd. by: Novartis Singapore Pharmaceutical Manufacturing Pte. Ltd. 637461 Singapore Dist. by: Novartis Pharmaceuticals Corp. East Hanover, NJ 07936 www.Entresto.com 1-888-ENTRESTO (1-888-368-7378) © Novartis

Model container/carton/blister labels [Source: DARRTS; ANRPT-3; submitted 8/30/2018]







3.4 UNITED STATES PHARMACOPEIA (USP)

The [USP](#) was searched on 4/9/2020.

Table 2: United States Pharmacopeia (USP)				
	YES or NO	Date	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
Currently Official	NO		NA	NA
Not Yet Official	NO	NA	NA	NA

Reviewer Assessment:

Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labeling and labels? **NA**

Reviewer Comments:

None

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 4/9/2020.

Table 3 provides Orange Book patents for the Model Labeling NDA 207620 and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter Carve-out or None)
7468390	2023-11-27			IV	3/23/20	None
7468390*PED	2024-05-27					
8877938	2027-05-27			IV	3/23/20	None
8877938*PED	2027-11-27					
8796331	2023-01-14	U-1723	TREATMENT OF HEART FAILURE	IV	3/23/20	None
8796331*PED	2023-07-14					
8404744	2023-01-14			IV	3/23/20	None
8404744*PED	2023-07-14					
9388134	2026-11-08	U-1723	TREATMENT OF HEART FAILURE	IV	3/23/20	None
9388134*PED	2027-05-08					
8101659	2023-01-14			IV	3/23/20	None
8101659*PED	2023-07-14					

Reviewer Assessment:

Is the applicant's "patent carve out" acceptable? **NA**

Reviewer Comments:

None

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact (enter Carve-out or None)
NCE	7/7/2020	New Chemical Entity	MSN Laboratories Private Ltd commits not to market this product until the expiration of the above exclusivity.	7/8/2019	None
NCE *PED	1/7/2021		MSN Laboratories Private Ltd commits not to market this product until the expiration of NCE*PED exclusivity.	3/3/2020	None
NPP	10/1/2022	New Patient Population	With respect to the exclusivity code "NPP *PED" expiring on April 01, 2023. The proposed labeling for the MSN product does not include information associated with the NPP*PED exclusivity.	3/3/2020	Carve-out
NPP *PED	4/1/2023				

Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **YES**

Reviewer Comments:

The Applicant revised their labeling accordingly to the BPCA model template that was provided to them. They stated that they plan on carving-out the NPP *PED exclusivity. Since the NPP and NPP *PED are associated, we interpret that the NPP exclusivity will be addressed the same way as the NPP *PED exclusivity.

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the inactive ingredients, dosage form description, package sizes, and manufacturer/distributor/packer statements of the Prescribing Information or Drug Facts for OTC products when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or Inactive Ingredients (OTC)? **NO**
 Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **NO**
 Are there changes to the manufacturer/distributor/packer statements? **NO**
 If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)

Previous Labeling Review	Currently Proposed	Assessment
Sacubitril and valsartan tablets are available as film-coated tablets for oral administration, 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. The tablet inactive ingredients are colloidal silicon dioxide, croscopovidone, croscarmellose sodium, magnesium stearate, microcrystalline cellulose and talc. The film-coat inactive ingredients are hypromellose, titanium dioxide, macrogol, talc and iron oxide red. The film-coat for the 24 mg of sacubitril and 26 mg of valsartan tablet and 97 mg of sacubitril and 103 mg of valsartan tablet also contains iron oxide black. The film-coat for the 49 mg of sacubitril and 51 mg of valsartan tablet also contains iron oxide yellow.	Sacubitril and valsartan tablets are available as film-coated tablets for oral administration, 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. The tablet inactive ingredients are colloidal silicon dioxide, croscopovidone, croscarmellose sodium, magnesium stearate, microcrystalline cellulose and talc. The film-coat inactive ingredients are hypromellose, titanium dioxide, macrogol, talc and iron oxide red. The film-coat for the 24 mg of sacubitril and 26 mg of valsartan tablet and 97 mg of sacubitril and 103 mg of valsartan tablet also contains iron oxide black. The film-coat for the 49 mg of sacubitril and 51 mg of valsartan tablet also contains iron oxide yellow.	Acceptable: No noted changes.

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products

Previous Labeling Review	Currently Proposed	Assessment																									
(b)(4)	Sacubitril/valsartan tablets are available as unscored, oval shaped, 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. All strengths are packaged in bottles as described below.	Acceptable: Revised as requested.																									
	<table><tr><th>Tablet</th><th>Color</th><th>Debossment</th><th colspan="2">NDC # 69539-XXX-XX</th></tr><tr><td>Sacubitril/Valsartan</td><td></td><td>"M" and</td><td>Bottle of 60</td><td>Bottle of 180</td></tr><tr><td>24 mg/26 mg</td><td>Purple</td><td>S1</td><td>166-60</td><td>166-18</td></tr><tr><td>49 mg/51 mg</td><td>Light yellow</td><td>S2</td><td>167-60</td><td>167-18</td></tr><tr><td>97 mg/103 mg</td><td>Light pink</td><td>S3</td><td>168-60</td><td>168-18</td></tr></table>		Tablet	Color	Debossment	NDC # 69539-XXX-XX		Sacubitril/Valsartan		"M" and	Bottle of 60	Bottle of 180	24 mg/26 mg	Purple	S1	166-60	166-18	49 mg/51 mg	Light yellow	S2	167-60	167-18	97 mg/103 mg	Light pink	S3	168-60	168-18
	Tablet		Color	Debossment	NDC # 69539-XXX-XX																						
	Sacubitril/Valsartan			"M" and	Bottle of 60	Bottle of 180																					
	24 mg/26 mg		Purple	S1	166-60	166-18																					
	49 mg/51 mg		Light yellow	S2	167-60	167-18																					
97 mg/103 mg	Light pink	S3	168-60	168-18																							
Store at 25°C (77°F), excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from moisture.																											

Table 7: Manufacturer/Distributor/Packer Statements

Previous Labeling Review	Currently Proposed	Assessment
--------------------------	--------------------	------------

Table 7: Manufacturer/Distributor/Packer Statements		
Manufactured by: MSN Laboratories Private Limited Telangana – 509 228, INDIA Distributed by: MSN Pharmaceuticals Inc. Piscataway, NJ 08854 -3714	Manufactured by: MSN Laboratories Private Limited Telangana – 509 228, INDIA Distributed by: MSN Pharmaceuticals Inc. Piscataway, NJ 08854 -3714	Acceptable: No noted changes.

5. COMMENTS/CONSULTS FOR OTHER DISCIPLINES

Describe questions, issues and consults sent to and/or received from other discipline(s) (e.g., OPQ, OB, DCR):

Refer to the Consult Screening flow chart to determine any necessary consults.

(For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue). Reminder: Refer to chemistry review to verify labeling section (per Chemistry-Labeling MOU) is complete. Refer to DCR review for combination product to verify if labeling comments were communicated to applicant.

Reviewer Comments:

None

6. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for all labeling pieces for this application.

For each row, you **MUST** choose an item “Final, Draft, or “NA”. If you enter “NA” under the second column, you do NOT need to enter “NA” for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	Packaging Sizes	Submission Received Date	Recommendation
Container	Final	24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg (60s and 180s count bottles)	10/30/2019	Satisfactory
Blister	NA			
Carton	NA			
(Other – specify)	NA			
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	Revision Date and/or Code	Submission Received Date	Recommendation
Prescribing Information	Draft	3/2020	3/3/2020	Satisfactory
Medication Guide	NA			
Patient Information	Draft	3/2020	3/3/2020	Satisfactory
SPL Data Elements		3/2020	3/3/2020	Satisfactory



Wan
Lee

Digitally signed by Wan Lee
Date: 4/23/2020 06:59:03AM
GUID: 582a2cfa001b51dba58dfaf180bcd09a



Betty
Turner

Digitally signed by Betty Turner
Date: 4/23/2020 07:39:29AM
GUID: 508da70600028acef381be737f7836a9

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	September 9, 2019
ANDA Number(s)	213748
Review Number	1
Applicant Name	MSN Laboratories Private Limited
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Sacubitril and Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg
Proposed Proprietary Name	None
Submission Received Date	July 8, 2019
Primary Labeling Reviewer	Wan Lee, PharmD
Secondary Labeling Reviewer	Refer to signature page
Review Conclusion ☐ ACCEPTABLE – No Comments ☐ ACCEPTABLE – Include Post Approval Comments ☒ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for Letter to Applicant ☐ Major Deficiency [†] – Refer to Labeling Deficiencies and Comments for Letter to Applicant [†] Theme - Choose an item. Justification for Major Deficiency - Choose an item. *Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.	
On Policy Alert List	☒ Yes ☐ No
Acceptable for Filing	☒ Yes ☐ No
Combined Insert/Outsert	☐ Yes ☒ No (If yes, indicate ANDA number)

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1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on September 9, 2019, based on your submission received July 8, 2019:

1. GENERAL COMMENTS

We note that the most current model labeling approved for your proposed drug product is not being used according to 21 CFR 314.94(8)(iv). Refer to Drugs@FDA: FDA Approved Drug Products, NDA 207620/S-013 approved on October 1, 2019, and revise accordingly.

2. CONTAINER LABEL

- a. We note that the RLD does not contain a Medication Guide but rather a Patient Information leaflet. We also note that in your submission, you have provided a similar document. (b)(4)
- b. Revise the (b)(4) statement to read "Each film-coated tablet contains XX mg of sacubitril and XX mg of valsartan." (note hyphen).
- c. We recommend revising your storage statement to read, "Store at 25°C (77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from moisture." (note revise "to" to "between").

3. PRESCRIBING INFORMATION

- a. There should not be white space between "HIGHLIGHTS OF PRESCRIBING INFORMATION" and the Highlights statement.
- b. HIGHLIGHTS and FULL PRESCRIBING INFORMATION: In the boxed warning, revise (b)(4) to the drug product, "sacubitril and valsartan tablets".
- c. (b)(4)
- d. DOSAGE FORMS AND STRENGTHS: To align with the RLD, we recommend including "unscored" as a characteristic of the drug product.
- e. USE IN SPECIFIC POPULATIONS, Lactation: In the last sentence of the "Data" subsection, ensure there is a space between "of valsartan".
- f. HOW SUPPLIED:
 - i. To align with the RLD, we recommend including "unscored" as a characteristic of the drug product.
 - ii. We recommend revising your storage statement to read, "Store at 25°C (77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]". Retain all other information.

4. PATIENT INFORMATION

- a. We recommend revising your established name to "Sacubitril and Valsartan Tablets" to be consistent throughout your labeling.
- b. Revise your proposed pronunciation of the non-proprietary name to conform to the phonetic pronunciation in the current USP Dictionary of USAN and International Drug Names (sak ue' bi tril and val sar' tan).

- c. To separate each section, we recommend using boxes or white space for easy readability. Please refer to RLD.

d.

(b)(4)

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission(s) received (add date).

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.3 POST APPROVAL REVISIONS

These comments will be addressed post approval (in the first labeling supplement review).

[Click here to enter text.](#)

2. LABELING REVIEW INFORMATION

2.1 REGULATORY INFORMATION

Are there any applicable issues in DLR's SharePoint Drug Facts? NO

If YES, please explain.

Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? YES

If YES, please explain.

CP	FDA-2019-P-1893	Entresto	sacubitril; valsartan tablets	Requests FDA to: (1) Require ANDAs that reference ENTRESTO to demonstrate API sameness; (2) Revise FDA's Draft Guidance document regarding sacubitril/valsartan oral tablets to recommend that API sameness be established by showing that the chemical structure of each active ingredient in the finished dosage form of a proposed generic is identical to the chemical structure of each active ingredient in the RLD, including all ionic bonds; (3) Further revise the Draft Guidance to include BE and PK requirements.	207620
----	-----------------	----------	-------------------------------	--	--------

No Approval Actions (AP/TA) can be taken prior to contacting Policy Lead

All disciplines can continue communications (CRL, IR/DRL); CC should contact Policy if related to CP

Is the drug product listed in the Susceptibility Test Interpretive Criteria web page? NO

Is there a mid-review cycle meeting (MRCM) task in Platform? NO

If YES, what is the proposed agenda from DLR for MRCM?

Click here to enter text.

Is there a Product Development or Pre-ANDA Submission Project under the ANDA Program? NO

If YES, review the meeting minutes and state the labeling impact, if any.

Click here to enter text.

2.2 MODEL LABELING

2.2.1 MODEL PRESCRIBING INFORMATION/DRUG FACTS LABELING (OTC)

Table 1: Review Model Labeling for Prescribing Information, Patient Labeling, or Drug Facts Labeling (OTC)
(Check the box used as the Model Labeling)

☒ **MOST RECENTLY APPROVED NDA MODEL LABELING**

(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so, enter the most recently approved ANDA labeling information as applicable.)

NDA#/Supplement# (S-000 if original): NDA 207620/S-013

Supplement Approval Date: October 1, 2019

Proprietary Name: Entresto

Established Name: sacubitril/valsartan tablets

Description of Supplement:

This Prior Approval supplemental new drug application, submitted in response to a Pediatric Written Request, supports a labeled indication for use of Entresto® for 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.

**Table 1: Review Model Labeling for Prescribing Information, Patient Labeling, or Drug Facts Labeling (OTC)
(Check the box used as the Model Labeling)**

OTHER IMPORTANT INFORMATION:

Supplement 16 (CBE-30 CMC supplement): PENDING; submission of carton labels

(b)(4)

Supplements 14 to 15 (CMC supplements): PENDING and Approved
No submission of labels; no impact on labeling.

Supplement 9 to 12 (CMC supplements): APPROVED (CR supplement 11)
No submission of labels; no impact on labeling.

☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING**

ANDA#/Supplement# (S-000 if original): Click here to enter text.

Supplement Approval Date: Click here to enter text.

Proprietary Name: Click here to enter text.

Established Name: Click here to enter text.

Description of Supplement: Click here to enter text.

☐ **TEMPLATE (e.g., BPCA, PREA, Carve-out):** Click here to enter text.

☐ **OTHER (Describe):**

2.2.2 MODEL CONTAINER LABELS

Model container/carton/blister labels (Source: DARRTS; ANRPT-4 submitted 8/30/2019)



EXP/LOT:

**Physician Sample
Not for Sale**

Entresto[®]
(sacubitril/valsartan)
tablets

24mg/26mg

Rx only 28 Tablets

NOVARTIS

Usual Dosage: See prescribing information.
Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F), [see USP controlled room temperature].
Protect from moisture.

Keep this and all drugs out of the reach of children.

Mfd. by: Novartis Singapore Pharmaceutical Manufacturing Pte. Ltd., 637461 Singapore
Dist. by: Novartis Pharmaceuticals Corp. East Hanover, NJ 07936

www.Entresto.com
1-888-ENTRESTO (1-888-368-7378)
©Novartis 0078-9659-50 121137 USS

EXP/LOT

GTIN: 00300780659208

3

0078-0659-20

8

NDC 0078-0659-20

Entresto[®]
(sacubitril/valsartan)
tablets

24mg/26mg

**Rx only
60 Tablets**

NOVARTIS

Usual Dosage: See prescribing information.
Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F), [see USP controlled room temperature].
Protect from moisture.

Keep this and all drugs out of the reach of children.

Mfd. by: Novartis Singapore Pharmaceutical Manufacturing Pte. Ltd., 637461 Singapore
Dist. by: Novartis Pharmaceuticals Corp. East Hanover, NJ 07936

www.Entresto.com
1-888-ENTRESTO (1-888-368-7378)
© Novartis 121252 US

EXP/LOT

GTIN: 00300780777674

3

0078-0777-67

4

NDC 0078-0777-67

Entresto[®]
(sacubitril/valsartan)
tablets

49mg/51mg

**Rx only
180 Tablets**

NOVARTIS

Usual Dosage: See prescribing information.
Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F), [see USP controlled room temperature].
Protect from moisture.

Keep this and all drugs out of the reach of children.

Mfd. by: Novartis Singapore Pharmaceutical Manufacturing Pte. Ltd., 637461 Singapore
Dist. by: Novartis Pharmaceuticals Corp. East Hanover, NJ 07936

www.Entresto.com
1-888-ENTRESTO (1-888-368-7378)
© Novartis 121255 US


 EXP/LOT:

Physician Sample
Not for Sale



Entresto[®]
 (sacubitril/valsartan)
 tablets

49mg/51mg

Rx only 28 Tablets

 **NOVARTIS**

Usual Dosage: See prescribing information.

Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F), [see USP controlled room temperature].

Protect from moisture.

Keep this and all drugs out of the reach of children.

Mfd. by: Novartis Singapore Pharmaceutical Manufacturing Pte. Ltd., 637461 Singapore

Dist. by: Novartis Pharmaceuticals Corp. East Hanover, NJ 07936

www.Entresto.com

1-888-ENTRESTO (1-888-368-7378)

©Novartis 0078-9777-50 121138 USS


 EXP/LOT:

NDC 0078-0777-20



Entresto[®]
 (sacubitril/valsartan)
 tablets

49mg/51mg

**Rx only
60 Tablets**

 **NOVARTIS**

Usual Dosage: See prescribing information.

Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F), [see USP controlled room temperature].

Protect from moisture.

Keep this and all drugs out of the reach of children.

Mfd. by: Novartis Singapore Pharmaceutical Manufacturing Pte. Ltd., 637461 Singapore

Dist. by: Novartis Pharmaceuticals Corp. East Hanover, NJ 07936

www.Entresto.com

1-888-ENTRESTO (1-888-368-7378)

© Novartis 121254 US


 EXP/LOT:

NDC 0078-0696-67



Entresto[®]
 (sacubitril/valsartan)
 tablets

97mg/103mg

**Rx only
180 Tablets**

 **NOVARTIS**

Usual Dosage: See prescribing information.

Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F), [see USP controlled room temperature].

Protect from moisture.

Keep this and all drugs out of the reach of children.

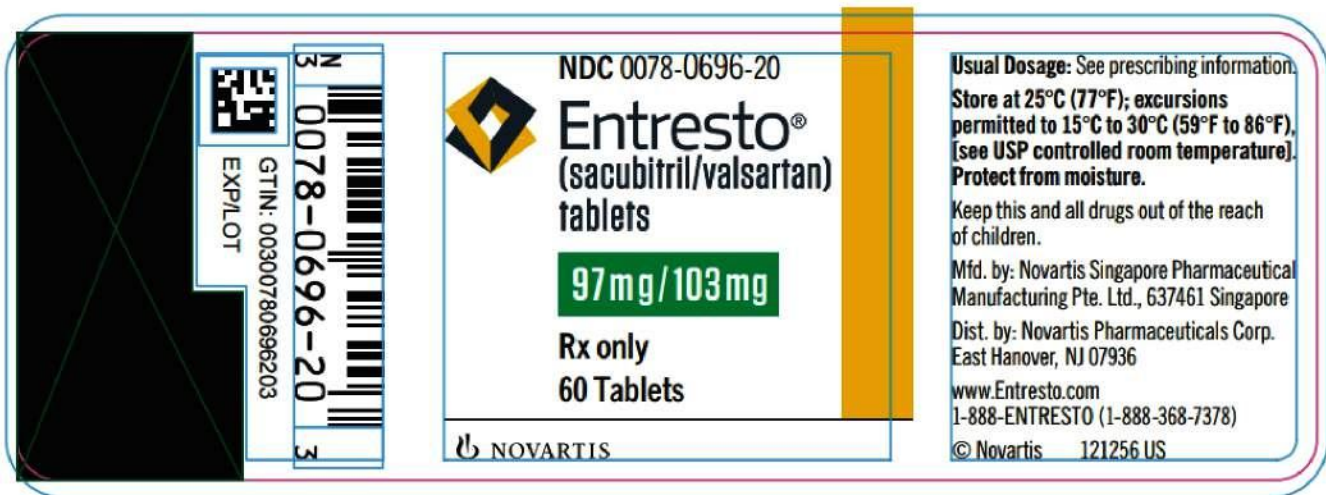
Mfd. by: Novartis Singapore Pharmaceutical Manufacturing Pte. Ltd. 637461 Singapore

Dist. by: Novartis Pharmaceuticals Corp. East Hanover, NJ 07936

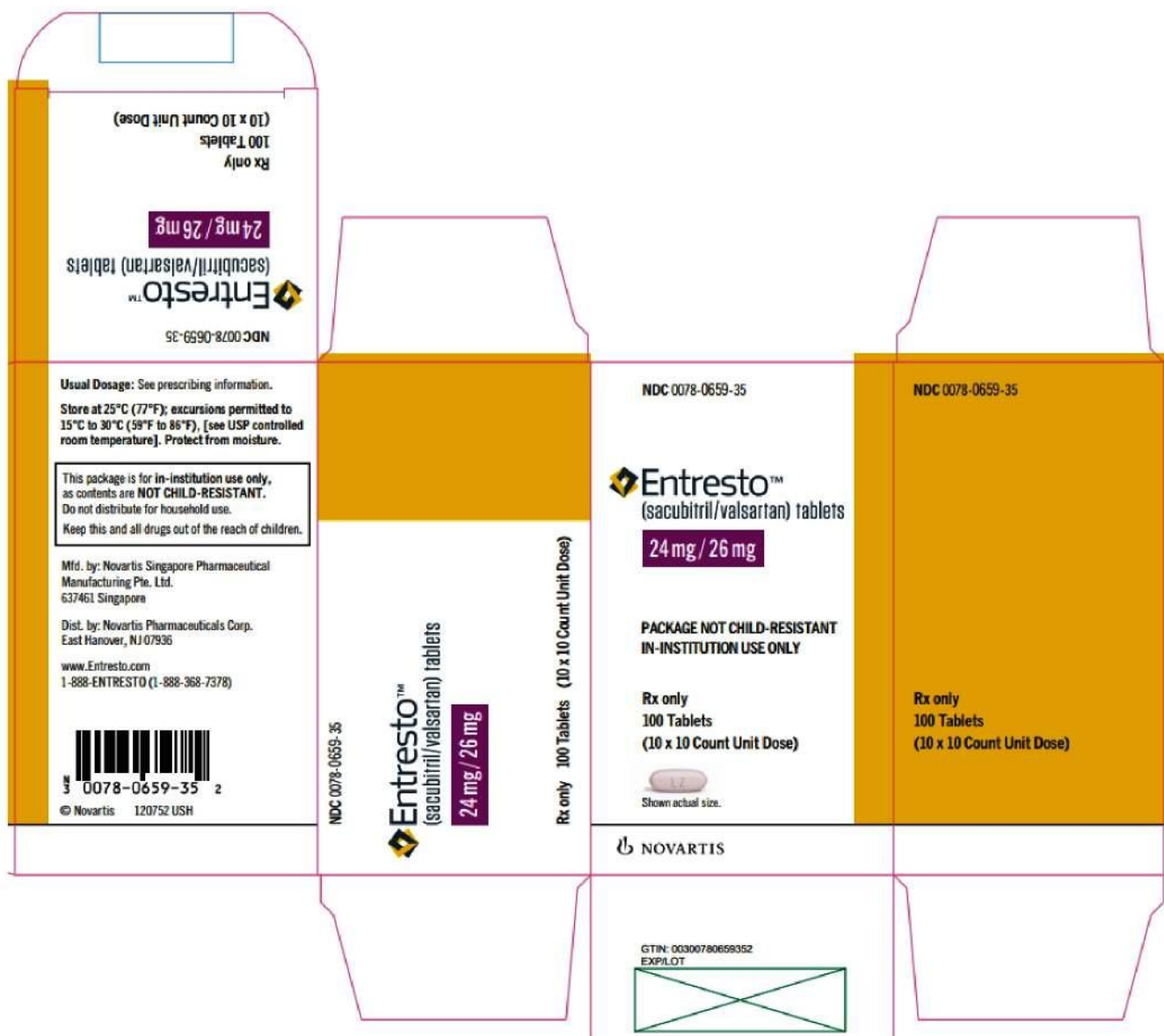
www.Entresto.com

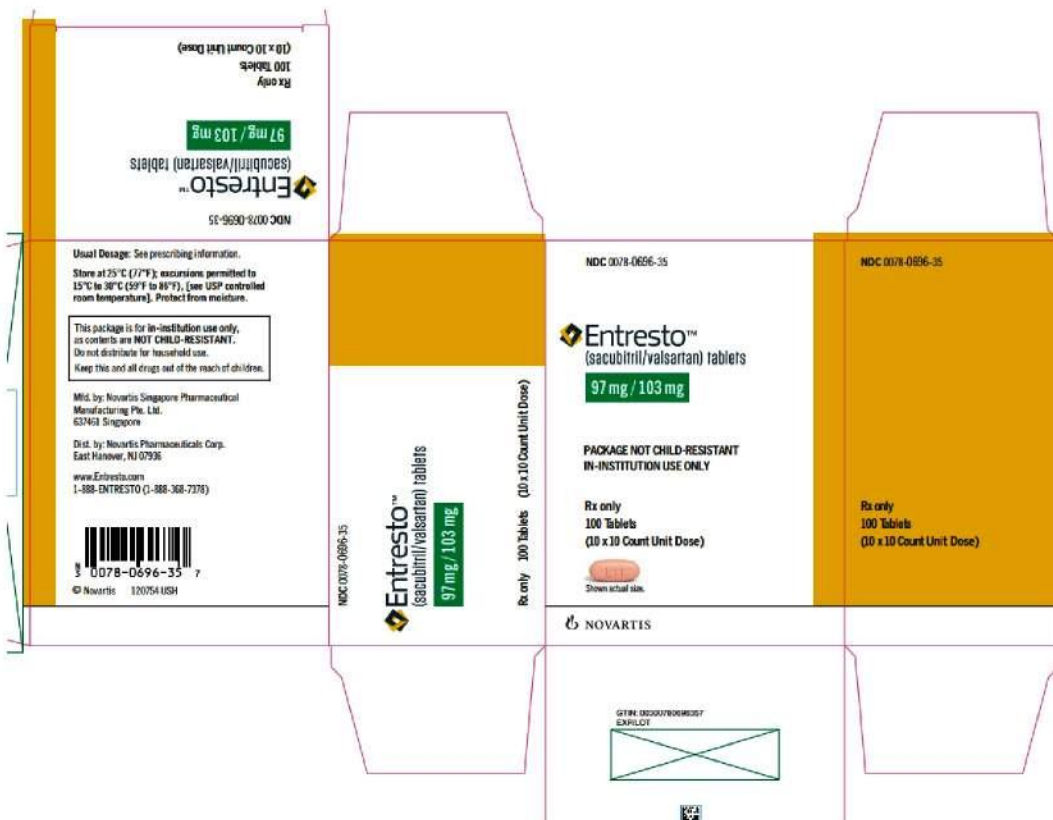
1-888-ENTRESTO (1-888-368-7378)

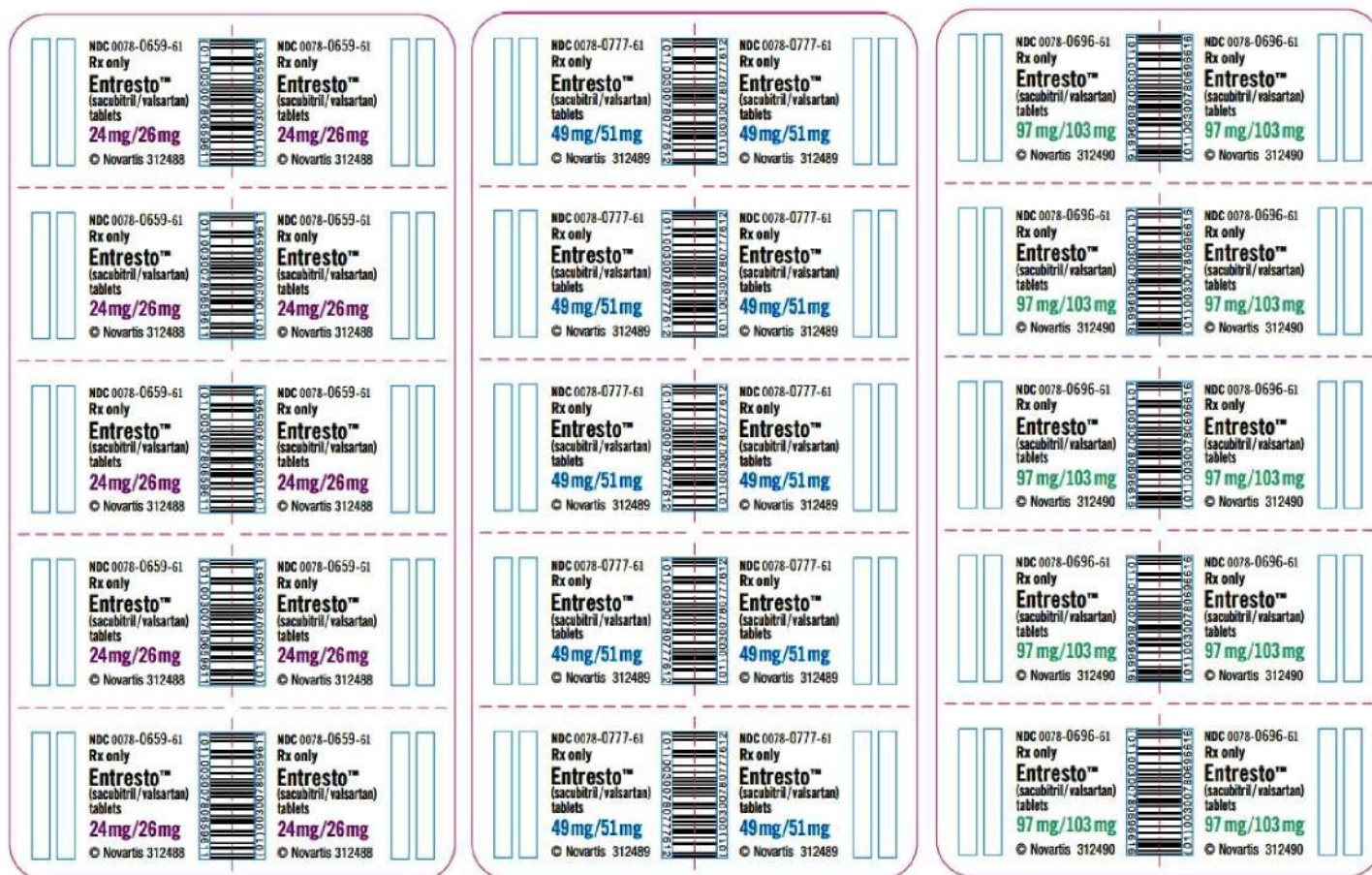
© Novartis 121257 US



Model container/carton/blister labels (Source: DARRTS; ANRPT-3 submitted 8/30/2018)







2.3 UNITED STATES PHARMACOPEIA (USP)

The [USP](#) was searched on 9/9/2019.

Table 2: USP

	YES or NO	Date	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
Currently Official	NO		NA	NA
Not Yet Official	NO	NA	NA	NA

2.4 PATENTS AND EXCLUSIVITIES

The [Orange Book](#) was searched on 10/9/2019.

Table 3 provides Orange Book patents for the Model Labeling (NDA 207620) and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 3: Impact of Model Labeling Patents on ANDA Labeling

Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter Carve-out or None)
7468390	2023-11-27			IV	7/8/2019	None
7468390*PED	2024-05-27					
8877938	2027-05-27			IV	7/8/2019	None

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
8877938*PED	2027-11-27					
8796331	2023-01-14	U-1723	TREATMENT OF HEART FAILURE	IV	7/8/2019	None
8796331*PED	2023-07-14					
8404744	2023-01-14			IV	7/8/2019	None
8404744*PED	2023-07-14					
9388134	2026-11-08	U-1723	TREATMENT OF HEART FAILURE	IV	7/8/2019	None
9388134*PED	2027-05-08					
8101659	2023-01-14			IV	7/8/2019	None
8101659*PED	2023-07-14					

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact (enter Carve-out or None)
NCE	2020-07-07	NEW CHEMICAL ENTITY	MSN Laboratories Private Ltd commits not to market this product until the expiration of the above exclusivity.	7/8/2019	None

2.5 MANUFACTURER, DISTRIBUTOR, AND/OR PACKER

Table 5: Comparison of Manufacturer/Distributor/Packer Labeling Statements		
Name and Address of ANDA Manufacturer/Distributor/Packer (Module 3.2.P.3)	Name and Address on ANDA Container/Carton	Name and Address on ANDA Prescribing Information
(b)(4)		Manufactured by: MSN Laboratories Private Limited Telangana – 509 228, INDIA Distributed by: MSN Pharmaceuticals Inc. Piscataway, NJ 08854 -3714

3. ASSESSMENT OF ANDA LABELING AND LABELS

Is this product Rx or OTC? Please check one.

- ☒ Rx Product (If Rx, skip 3.2 OTC DRUG PRODUCT.)
☐ OTC Product (If OTC, skip 3.1 RX DRUG PRODUCT.)

3.1 RX (PRESCRIPTION) DRUG PRODUCT

3.1.1 RX: PRESCRIBING INFORMATION

Reviewer Assessment:

Is the Prescribing Information same as the model labeling, except for differences allowed under [21 CFR 314.94\(a\)\(8\)](#)? **NO**

Is the established name the same as the USP monograph title appearing in section 2.3? **NA**

Is the established name the same as the RLD's nonproprietary name? **YES**

If NO is answered to EITHER of the 2 questions above, then advise firm to revise to the USP name (if applicable) and include justification language under Reviewer Comments.

Does the Model Labeling have combined insert labeling for multiple NDAs or dosage forms? **NO**

Is the applicant's "patent carve out" acceptable? **NA**

Is the applicant's "exclusivity carve out" acceptable? **NA**

Is the Manufacturer/Distributor/Packer statement acceptable? **YES**

Is there a Pregnancy Registry for the NDA RLD? **NO** (If YES, determine if it is required for the ANDA and provide assessment under Reviewer Comments.)

For antiretroviral applications, did the applicant state its intent to join the Antiretroviral Pregnancy Registry (APR) upon full approval? **NA**

Reviewer Comments:

- a. We note that supplement-13 was approved on October 1, 2019. Therefore, at the time of this review, the most current RLD labeling was not submitted by the applicant. We will ask that the applicant use the last approved labeling. In addition, we note that supplement-13 is an efficacy supplement adding a pediatric indication. Exclusivity was granted on September 26, 2019. Currently in the Orange Book, there are additional pediatric extensions (6 months with no patent use codes attached to them). See section 2.4. (b)(4)

(b)(4)

In the meantime, we will continue with our assessment with the current submission.

- a. See comments above.

3.1.1.1 RX: DESCRIPTION

Table 6: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section

Model Labeling	ENTRESTO is available as film-coated tablets for oral administration, 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. The tablet inactive ingredients are microcrystalline cellulose, low-substituted hydroxypropylcellulose, crospovidone, magnesium stearate (vegetable origin), talc, and colloidal silicon dioxide. The film-coat inactive ingredients are hypromellose, titanium dioxide (E 171), Macrogol 4000, talc, and iron oxide red (E 172). The film-coat for the 24 mg of sacubitril and 26 mg of valsartan tablet and the 97 mg of sacubitril and 103 mg of valsartan tablet also contains iron oxide black (E 172). The film-coat for the 49 mg of sacubitril and 51 mg of valsartan tablet contains iron oxide yellow (E 172).
ANDA Labeling	Sacubitril and valsartan tablets are available as film-coated tablets for oral administration, 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. The tablet inactive ingredients are colloidal silicon dioxide, crospovidone, croscarmellose sodium, magnesium stearate, microcrystalline cellulose and talc. The film-coat inactive ingredients are hypromellose, titanium dioxide, macrogol, talc and iron oxide red. The film-coat for the 24 mg of sacubitril and 26 mg of valsartan tablet and 97 mg of sacubitril and 103 mg of valsartan tablet also contains iron oxide black. The film-coat for the 49 mg of sacubitril and 51 mg of valsartan tablet also contains iron oxide yellow.

Reviewer Assessment:

Are the inactive ingredients accurate? **PENDING DRUG PRODUCT REVIEW**

For products required to be qualitatively and quantitatively the same in regards to active and inactive ingredients (Q1/Q2), are the ANDA ingredients consistent with the Model Labeling? **NA**

Does any inactive ingredient require special warnings, precautions, or labeling statements? **NO**

Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labeling? **NA**

If the labeling includes a “Does not contain...” statement, is it acceptable/allowed? **NA** Has the statement been verified by drug product reviewer? **NA**

Reviewer Comments:

None

3.1.1.2 RX: HOW SUPPLIED/STORAGE AND HANDLING

Table 7: Comparison of Model Labeling to ANDA Labeling

Model Labeling	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. All strengths are packaged in bottles and unit dose blister packages (10 strips of 10 tablets) as described below.				
	Tablet	Color	Debossment	NDC # 0078-XXXX-XX	
	Sacubitril/Valsartan		"NVR" and	Bottle of 60	Blister Packages of 100
	24 mg/26 mg	Violet white	LZ	0659-20	0659-35
	49 mg/51 mg	Pale yellow	L1	0777-20	0777-35
	97 mg/103 mg	Light pink	L11	0696-20	0696-35
	Store at 25°C (77°F) with excursions between 15°C and 30°C (59°F and 86°F) permitted [see USP Controlled Room Temperature]. Protect from moisture.				
ANDA Labeling	(b)(4)				

Reviewer Assessment:

Are all of the submitted labels and labeling consistent with the How Supplied section? **YES**

Is the description (e.g., scoring, color, imprint) of the finished product in the HOW SUPPLIED section accurate? **PENDING DRUG PRODUCT REVIEW**

Does the ANDA require the same color coding as the Model? **NO**

Is there any difference in scoring configuration between the ANDA and the Model Labeling? **NO**

Are the packaging sizes and configurations acceptable as compared to the Model Labeling? **YES**

If the packaging configuration is different than the Model Labeling, does it require addition or deletion of labeling statements? **NA**

Is the storage or dispensing statement acceptable as compared to the Model Labeling? **YES**

Is the storage or dispensing statement acceptable as compared to the USP? **NA**

Reviewer Comments:

We will recommend including “unscored” as an identifying characteristic of the drug product to be consistent with the RLD.

3.1.2 RX: MEDICATION GUIDE

Is Medication Guide required? **NO**

If YES go to Reviewer Assessment below, if NO go to section 3.1.3.

Reviewer Assessment:

Was Medication Guide submitted? **NO**

Is the Medication Guide same as the model labeling, except for allowable differences? **NA**

Has the Applicant committed to provide a sufficient number of medication guides? **NA**

Is the phonetic spelling of the proprietary or established name present? **NA**

Is FDA 1-800-FDA-1088 phone number included? **NA**

Reviewer Comments:

[Click here to enter text.](#)

3.1.3 RX: OTHER PATIENT LABELING

Are other patient labeling required? **YES**

If YES go to Reviewer Assessment below, if NO go to section 3.1.4.

Reviewer Assessment:

Was other patient labeling submitted? **YES**

Is the patient labeling the same as the model labeling, except for allowable differences? **NO**

Reviewer Comments:

See comments above.

3.1.4 RX: CONTAINER LABEL

Was container label (other than Blisters) submitted? **YES**

(For BLISTER labels go to section 3.1.5.)

Reviewer Assessment:

Is the established name acceptable? **YES**

Is title case used in expressing the established name? **YES**

Does labeling comply with Tall Man lettering recommendations found on [FDA webpage](#)? **NA**

If the container label is too small to contain all required information, does it meet the “too small” exemption found in [21 CFR 201.10\(i\)](#)? **NA**

Are established name (proprietary name, if applicable) and strength the most prominent information on the Principal Display Panel? **YES**

Is the following information properly displayed?

Net quantity statement: **YES**

Route(s) of administration (other than oral): **NA**

Warnings (if any) or cautionary statements (if any): **NA**

Medication Guide Pharmacist instructions per [21 CFR 208.24\(d\)](#): **NO**

[Controlled substance symbol](#): **NA**

Usual Dosage statement: **YES**

Product strength equivalency statement: **NA**

NDC: **YES**

Bar code per [21 CFR 201.25\(c\)\(2\)](#): **YES**

Is the Manufacturer/Distributor/Packager statement acceptable? **YES**

Are the USP recommendations and/or differences in test methods (e.g., organic impurities, assay) reflected on the label(s)? **NA**

Is the storage or dispensing statement consistent with the How Supplied section of the insert? **NO**

Does any inactive ingredient require special warnings, precautions, or labeling statements? **NO**

Are multiple strengths differentiated by use of different color or other acceptable means? **YES**

Are the labels of related products differentiated to avoid selection errors? **NA**

Does the ANDA require the same color coding as the Model? **NO**

Are requirements met for the required label statements ([21 CFR 201.15](#) and [21 CFR 201.100](#))? **YES**

Reviewer Comments:

a. We will ask the Applicant to revise the storage statement to be consistent with the container labels.

b.

(b)(4)

3.1.4.1 RX: CONTAINER LABEL FOR PARENTERAL SOLUTIONS

Is container for parenteral solution? **NO**

If YES go to Reviewer Assessment below, if NO go to section 3.1.4.2.

Reviewer Assessment:

Is the product strength expressed as total quantity per total volume followed by the concentration per milliliter (mL), as described in the USP General Chapter <7> Labeling **NA**

If volume is less than 1 mL, is strength per fraction of a milliliter the only expression of strength? **NA**

Is the quantity or proportion of all inactive ingredients listed on label as required under [21 CFR 201.100\(b\)\(5\)\(iii\)](#)? **NA**

Reviewer Comments:

[Click here to enter text.](#)

3.1.4.2 RX: CONTAINER LABEL FOR SOLID INJECTABLE

Is container for solid injectable (other than Pharmacy Bulk Package)? **NO**

If YES go to Reviewer Assessment below, if NO go to section 3.1.4.3.

Reviewer Assessment:

Is the strength in terms of the total amount of drug per vial? **NA**

Are instructions for reconstitution and resultant concentration provided, if space permits? **NA**

Is the quantity or proportion of all inactive ingredients listed on label as required under [21 CFR 201.100\(b\)\(5\)\(iii\)](#)? **NA**

Reviewer Comments:

[Click here to enter text.](#)

3.1.4.3 RX: CONTAINER LABEL FOR PHARMACY BULK PACKAGE

Is container a [Pharmacy Bulk Package](#) (parenteral preparations for admixtures)? **NO**

If YES go to Reviewer Assessment below, if NO go to section 3.1.5.

Reviewer Assessment:

Is the strength in terms of the total amount of drug per vial? **NA**

Is there a prominent, boxed declaration reading “Pharmacy Bulk Package – Not for Direct Infusion” on the principal display panel following the expression of strength? **NA**

Does the container label include graduation marks? **NA**
Are instructions for reconstitution and resultant concentration provided, if space permits? **NA**
Does label contain the required information on proper aseptic technique including time frame in which the container may be used once it has been entered? **NA**
Is the quantity or proportion of all inactive ingredients listed on label as required under [21 CFR 201.100\(b\)\(5\)\(iii\)](#)? **NA**

Reviewer Comments:

[Click here to enter text.](#)

3.1.5 RX: UNIT DOSE BLISTER LABEL

Is container a Unit Dose Blister Pack? **NO**
If YES go to Reviewer Assessment below, if NO go to section 3.1.6.

Reviewer Assessment:

Does each blister include only one dosage unit (e.g., one tablet, one capsule)? **NA**
Do proprietary name, established name, strength, bar code, and manufacturer/distributor/packer appear accurately on each blister cell? **NA**

Reviewer Comments:

[Click here to enter text.](#)

3.1.6 RX: CARTON (OUTER OR SECONDARY PACKAGING) LABELING

Was carton labeling submitted? **NO**
If YES go to Reviewer Assessment below, if NO go to section 3.3.

Reviewer Assessment:

Are the answers to the Container Label questions the same for the Carton Labeling? **NA** If no, please explain the differences in the Reviewer Comments section.
If container is too small or otherwise unable to accommodate a label with enough space to include all required information, is all required information present on the carton labeling? **NA**

Reviewer Comments:

[Click here to enter text.](#)

3.2 OTC (OVER THE COUNTER) DRUG PRODUCT

3.2.1 OTC: LABELING THAT INCLUDES DRUGS FACTS INFORMATION

Reviewer Assessment:

Is Drug Facts Labeling format acceptable per [21 CFR 201.66](#)? **CLICK HERE**
Does “Questions?” have a toll-free number no less than 6 pt. font size per [21 CFR 201.66\(c\)\(9\)](#) or “1-800-FDA-1088” per [21 CFR 201.66 \(c\)\(5\)\(vii\)](#)? **CLICK HERE**
Did firm submit a Labeling Format Information Table to evaluate the font size? **CLICK HERE**
Is the applicant’s “patent carve out” acceptable? **CLICK HERE**
Is the applicant’s “exclusivity carve out” acceptable? **CLICK HERE**
Is the established name for this ANDA acceptable? **CLICK HERE**
Is title case used in expressing the established name? **CLICK HERE**
Are established name (proprietary name, if applicable) and strength the most prominent information on the Principal Display Panel? **CLICK HERE**
Is the following information properly displayed?
Pharmacological category: **CLICK HERE**
Net quantity statement: **CLICK HERE**

Route(s) of administration (other than oral): [CLICK HERE](#)
 Warnings (if any) or cautionary statements (if any): [CLICK HERE](#)
 NDC: [CLICK HERE](#)
 Bar code per [21 CFR 201.25\(c\)\(2\)](#): [CLICK HERE](#)

Is the Manufacturer/Distributor/Packager statement acceptable? [CLICK HERE](#)
 Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labeling? [CLICK HERE](#)
 Is the storage statement acceptable? [CLICK HERE](#)
 Does any inactive ingredient require special warnings, precautions, or labeling statements? [CLICK HERE](#)
 Are multiple strengths differentiated by use of different color or other acceptable means? [CLICK HERE](#)
 Are the labels of related products differentiated to avoid selection errors? [CLICK HERE](#)

Reviewer Comments:
[Click here to enter text.](#)

3.2.1.1 OTC: INACTIVE INGREDIENTS COMPARISON

Table 8: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section

Model Labeling	Click here to enter text.
ANDA Labeling	Click here to enter text.

Reviewer Assessment:

Are the inactive ingredients accurate? [CLICK HERE](#)
 Are the inactive ingredients listed in alphabetical order? [CLICK HERE](#)
 For products required/recommended to be qualitatively and quantitatively the same in regards to active and inactive ingredients (Q1/Q2), are the ANDA ingredients consistent with the Model Labeling? [CLICK HERE](#)
 Does any inactive ingredient require special warnings, precautions, or labeling statements? [CLICK HERE](#)
 If the labeling includes a “Does not contain...” statement, is it acceptable/allowed? [CLICK HERE](#) Has the statement been verified by drug product reviewer? [CLICK HERE](#)

Reviewer Comments:
[Click here to enter text.](#)

3.2.1.2 OTC: HOW SUPPLIED AND STORAGE INFORMATION

Table 9: Comparison of Model Labeling to ANDA finished product

Model Labeling	Description of Finished Product (Source: Click here to enter text.) Click here to enter text.
	Package Configurations (Source: Click here to enter text.) Click here to enter text.
	Storage Conditions (Source: Click here to enter text.) Click here to enter text.

Table 9: Comparison of Model Labeling to ANDA finished product

ANDA	Description of Finished Product (Source: Click here to enter text.) Click here to enter text.
	Package Configurations (Source: Click here to enter text.) Click here to enter text.
	Storage Conditions (Source: Click here to enter text.) Click here to enter text.

Reviewer Assessment:

Is the description ([scoring](#), color and [imprint](#)) of the finished product consistent with the Drug Product Quality submission? **CLICK HERE**

Is there any difference in scoring configuration between the ANDA and the Model Labeling? **CLICK HERE**

Are the packaging sizes and configurations acceptable as compared to the Model Labeling? **CLICK HERE**

If the packaging configuration is different than the Model Labeling, does it require addition or deletion of labeling statements? **CLICK HERE**

Is the storage statement acceptable as compared to the Model Labeling? **CLICK HERE**

Is the storage statement acceptable as compared to USP? **CLICK HERE**

Reviewer Comments:

[Click here to enter text.](#)

3.2.2 OTC: PATIENT LABELING

Is patient labeling required? **CLICK HERE**

If YES go to Reviewer Assessment below, if NO go to section 3.3.

Reviewer Assessment:

Was patient labeling submitted? **CLICK HERE**

Is the patient labeling the same as the model labeling, except for allowable differences? **CLICK HERE**

Reviewer Comments:

[Click here to enter text.](#)

3.3 CONTAINER/CLOSURE

Reviewer Assessment:

Describe container closure (e.g., 30s CRC, 100s non-CRC) and cite source of information in **Reviewer Comments** text box.

Is the use of a child-resistant closure (CRC) or non-CRC appropriate? **YES**

Are the tamper evident requirements met for [OTC](#), [Ophthalmic](#) and [Controlled Substances](#) **NA**

For ophthalmic products:

Does this ophthalmic product cap color match [the American Academy of Ophthalmology \(AAO\) packaging color-coding](#) scheme? **NA**

For parenteral products:

Is there text on the cap/ferrule overseal of this injectable product? **NA**

If YES, does text comply with the recommendations in USP General Chapter <7> Labeling? **NA**

What is the cap color? **NA**

NOTE: Black closure system is prohibited, except for Potassium Chloride for Injection Concentrate.

Reviewer Comments: 60s and 180s: CRC

3.2.P.7.1 Summary of Container/Closure System

(b)(4)

3.4 CALCULATIONS FOR CONTENTS AND VERIFICATION OF ALUMINUM CONTENT

Is calculation of ingredient(s) or verification of aluminum content required? **NO**

Table 10: Ingredients

Ingredient	Stated Content	Location of the Information
Click here to enter text.	Click here to enter text.	Click here to enter text.

Reviewer Assessment:

Are the stated contents in the table above acceptable? **CLICK HERE**

Aluminum content in small volume parenterals, large volume parenterals, and pharmacy bulk packages, which are used in TPNs, need to be in the labeling per [21 CFR 201.323](#).

Did the drug product reviewer verify the aluminum content? **CLICK HERE**

Are the labeling requirements met per [21 CFR 201.323](#)? **CLICK HERE**

Reviewer Comments:

[Click here to enter text.](#)

3.5 STRUCTURED PRODUCT LABELING (SPL) DATA ELEMENTS

Was SPL submitted? **YES**

Table 11: ANDA Tablet/Capsule Size and Imprint

Tablet/Capsule Strength	ANDA Tablet/Capsule Size (mm) and imprint code from SPL	ANDA Tablet/Capsule Size (mm) and imprint code (Cite source: e.g., Description and Composition of the Drug in 3.2.P.1)
24 mg/26 mg	10 mm / M;S1	10 mm / M;S1
49 mg/51 mg	13 mm / M;S2	13 mm / M;S2
97 mg/103 mg	15 mm / M;S3	15 mm / M;S3

Reviewer Assessment:

Are the data elements (strength, inactive ingredients, product characteristics, packaging etc.) consistent with the information submitted in the ANDA labeling? **YES**

Reviewer Comments:

Module 3.2.P.1

3.2.P.1 Description and Composition of the Drug Product

Table 1: Description of Dosage Form

Strength	Product Description
24 mg/ 26 mg	Purple colored, oval shaped, biconvex, film coated tablets one side debossed with 'M' and other side debossed with 'S1' (b)(4)
49 mg/51 mg	Light yellow to yellow colored, oval shaped, biconvex, film coated tablets one side debossed with 'M' and other side debossed with 'S2'' (b)(4)
97 mg/ 103 mg	Light pink to pink colored, oval shaped, biconvex, film coated tablets one side debossed with 'M' and other side debossed with 'S3'' (b)(4)

3.2.P.1 Description and Composition of the Drug Product	Module 3: Quality
---	-------------------

(b)(4)

4. COMMENTS FOR OTHER DISCIPLINES

Describe questions/issue(s) sent to and/or received from other discipline(s) (e.g., OPQ, OB):

(For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue)

Reviewer Comments:

None

5. SPECIAL CONSIDERATIONS

None

6. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Table 12: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	Packaging Sizes	Submission Received Date	Recommendation
Container	Final	24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg (60s and 180s count bottles)	July 8, 2019	Revise
Blister	NA			
Carton	NA			
(Other – specify)	NA			
Table 13 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	Revision Date and/or Code	Submission Received Date	Recommendation
Prescribing Information	Draft	July 2019	July 8, 2019	Revise
Medication Guide	NA			
Patient Information	Draft	July 2019	July 8, 2019	Revise
SPL Data Elements	NA	July 2019	July 8, 2019	Satisfactory



Wan
Lee

Digitally signed by Wan Lee
Date: 10/09/2019 01:45:04PM
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Betty
Turner

Digitally signed by Betty Turner
Date: 10/15/2019 11:21:27AM
GUID: 508da70600028acef381be737f7836a9

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 213748

CHEMISTRY REVIEW(s)

ANDA Executive Summary

1. Application/Product Information

ANDA Number.	213748		
Review Cycle #	05		
Applicant Name	MSN Laboratories Private Limited		
Drug Product Name	Sacubitril and Valsartan		
Dosage Form. (click (+) for more than one)	Tablet		
Proposed Strength(s)	24 mg/26 mg, 49 mg /51 mg and 97 mg/103 mg		
Route of Administration (click (+) for more than one)	Oral		
Maximum Daily Dose	sacubitril 97 mg and valsartan 103 mg x 2/day		
Rx/OTC Dispensed	Rx		
Proposed Indication	Sacubitril and valsartan tablet is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (b)(4) and reduced ejection fraction.		
Drug Product Description	Refer to 3.2.P.1		
Co-packaged product information	N/A		
Device information, if any:	N/A		
Storage Temperature/ Conditions	Store at 25°C (77°F), excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from moisture.		
Review Team	Discipline	Primary	Secondary
	<i>Drug Substance</i>	Behnam Abdolalizadeh	Mayra Pineiro-Sanchez

	<i>Drug Product/ Labeling</i>	Behnam Abdolalizadeh	Mayra Pineiro-Sanchez
	<i>Manufacturing</i>	Amit Kokate	Jean Tang R05: Vaikunth Prabhu
	<i>Biopharmaceutics</i>	Ho-Pi Lin	N/A
	<i>Microbiology</i>	N/A	N/A
	<i>Other (specify):</i>	N/A	N/A
	<i>RBPM</i>	Candice Cottle-Delisle R05: Jennifer Nguyen	
	<i>ATL</i>	Mayra Pineiro-Sanchez	
Consults	Discipline Consulted	Recommendation	Date

2. Submission Document(s) Reviewed

Submission(s) Assessed	Documents Date	Disciplines Affected
Original/Initial Submission	07/08/2019	All
Labeling-response to DRL	10/30/2019	Labeling
Quality/Response to Discipline Review Letter	02/27/2020	Quality
Resubmission/After Action- Complete Response	08/19/2020	Quality
Quality/Response To Information Request	08/28/2020	Quality
CR Response	02/09/2022	Quality
IR response	02/23/2022	Quality
CR Response	12/27/2022	Quality/Labeling
Quality/Response To Information Request	07/06/2023	Quality
CR Response	05/02/2024	Quality/Labeling

3. Related/Supporting Documents

a. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Assessor/ Comments
(b)(4)	II	(b)(4)	Sacubitril and Valsartan	Adequate	07/12/2023	R05
	II		(b)(4)	Adequate	02/09/2022	
	II			Adequate	04/05/2022	
	IV					
	IV					
	IV					
	III					Refer to 3.2.P.7
(b)(4)						

b. Other Documents: *IND, RLD, RS, Approved ANDA*

Document	Application Number	Description
RLD	NDA 207620	ENTRESTO®

4. Final Overall recommendation – Approval

Deficiencies (if applicable):

Overall Quality Deficiencies - Optional (*Deficiencies that affect multiple sub-disciplines; for subheadings use the format shown, for all deficiencies.*)

Drug Substance Deficiencies

Drug Product Deficiencies

Labeling Deficiencies (*Please contact OGD if you identify any Labeling deficiencies with your comments*)

Manufacturing Deficiencies

Biopharmaceutics Deficiencies

Microbiology Deficiencies

Other Deficiencies (Specify discipline, such as Environmental. For consults such as Biostatistics, PharmTox, CDRH, Clinical, etc., include consult type and specify Quality discipline – example: **Pharm/Tox consult for Drug Product**)

Additional Comments:

In addition to responding to the deficiencies presented above, please note and acknowledge the following comment(s) in your response:

5. Basis for Recommendation

a. Summary of Rationale for Recommendation:

The ANDA submitted on the basis of NDA 207620 (RLD), ENTRESTO includes sufficient information to assure the identity, strength, purity, and quality of the drug product during the expiration dating period of 24 months. The applicant has provided acceptable raw material, in-process, and finished product controls and established an adequate dissolution specification (method and acceptance criteria) for routine quality control of the finished product. The overall facility assessment recommends approval and the labels have adequate quality information. Applicant states categorical exclusion from the requirement of Environmental Impact Analysis per 21 CFR 25.31. Therefore, from the quality perspective, this ANDA is recommended for approval.

NDSRI-impacted ANDA? No

(b)(4)

b. Recommendation by Subdiscipline:

Drug Substance: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view [Justification Statements](#))

1.

Drug Product: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view [Justification Statements](#))

1.

Quality Labeling: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view [Justification Statements](#))

1.

Manufacturing: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view [Justification Statements](#))

1.

Biopharmaceutics: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view [Justification Statements](#))

1.

Microbiology: N/A

Provide justification(s) (for major deficiencies only):
(Click link to view [Justification Statements](#))

1.

Environmental: N/A

Provide justification(s) (for major deficiencies only):
(Click link to view [Justification Statements](#))

1.

6. Life-Cycle Considerations

**Established Conditions per ICH Q12: No
Comments:**

**Comparability Protocols (PACMP): No
Comments:**

Additional Comments:



Mayra
Pineiro Sanchez

Digitally signed by Mayra Pineiro Sanchez
Date: 6/11/2024 04:47:59PM
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RECOMMENDATION

☐ Complete Response-Major
☐ Complete Response-Minor
☐ Discipline Review Letter (DRL)
☐ Information Request—IR x Days
☒ Approval

ANDA 213748 Assessment Cycle #04

Drug Product Name	Sacubitril and Valsartan Tablets
USP Monograph	☐ Yes ☒ No
Strength	24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg
Dosage Form	Tablets
Route of Administration	Oral
Rx/OTC Dispensed	☒ Rx ☐ OTC
ANDA Applicant	MSN Laboratories Private Limited
Drug Product Manufacturer	☒ Same as the Applicant ☐ Different from the Applicant (see below)
US agent, if applicable	☐ N/A ☒ (See Below) MSN Pharmaceuticals Inc. 20 Duke Road, Piscataway, NJ 08854-3714
Proposed Indication	Sacubitril and Valsartan Tablets indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (b)(4) and reduced ejection fraction.

Submission(s) Assessed	Document Date	Discipline(s) Affected
IR Response	7/6/2023	Quality
CR 03	12/27/2022	Quality
CR 02	2/9/2022	Quality
CR 01	8/19/2020	Quality
Amendment-Response to DRL	2/27/2020	Quality
Original	7/8/2019	All
Labeling-Response to Discipline Review Letter*	10/30/2019	Labeling

*Preparation of oral suspension added in label to be in line with RLD, but no supporting quality information provided

Original & DRL assessed by 1ry: Qiuxia Wang; QAL: Raghu Samy
 Submission CR 01 and CR 02 assessed by B. Abdolizadeh
 Submission CR 03 assessed by B. Abdolizadeh in review R04
 Submission IR response assessed by B. Abdolizadeh in review R04

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QUALITY ASSESMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Reviewed	Comments
(b)(4)	II	(b)(4)	Sacubitril and Valsartan	Adequate, R05	07/12/2023	D. Yu
	II			Adequate, R04	02/09/2022	D. Yu
	II		(b)(4)	Adequate, R05	04/05/2022	D. Johnson
	Other DMF: ☐ N/A ☒ (See Below)					
	III	(b)(4)				
	III					
	III					
	III					
	III					
	III					
III						
III						
IV						
IV						
IV						
Other						

(b)(4)

B. OTHER DOCUMENTS: IND, RLD, RS, Approved ANDA

Document	Application Number	Brand Name	Description
NDA	207620	ENTRESTO®	Sacubitril and Valsartan Tab, 24/26, 49 /51, 97 /103 mg

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH-ODE	N/A			
CDRH-OC	N/A			
Clinical	N/A			
Other	N/A			

Review of Firm's Response to Deficiencies

Review of Amendment Dated 7/6/2023

This amendment is in response to complete response letter was issued on June 29, 2023.

The following link is for the responses to CR deficiencies:

[ANDA213748 \(213748 - 0014 - \(15\) - 2023-07-06 - ORIG-1 /Multiple Categories/Subcategories\) - response-to-ir-0014](#)

Comment 1:

(b)(4)

Applicant Response:

(b)(4)

Reviewer's Comment

adequate

Applicant has provided acceptable accuracy (b)(4)
(b)(4) in their provided method verification report.

Review of Firm's Response to Deficiencies

Review of Amendment Dated 12/27/2022

This amendment is in response to complete response letter was issued on 05/02/2022.

The following link is for the responses to CR deficiencies:

<\\CDSESUB1\EVSPROD\anda213748\0013\m1\us\response-to-crl-0013.pdf>

Comment 1:

(b)(4)

Applicant Response:

(b)(4)

DELETED PAGES INFORMATION SHEET

IT IS NOT REASONABLE TO SEGREGATE MEANINGFUL PORTIONS OF THE RECORD FOR RELEASE.

INFORMATION HAS BEEN WITHHELD IN ITS ENTIRETY IN ACCORDANCE WITH THE FOLLOWING EXEMPTIONS(S):

(b) (4)

5 U.S.C. 552 (b) (4) - trade secrets and commercial or financial information obtained from a person and privileged or confidential.

**OLDP Assessment Team: 1ry: Qiuxia Wang; QAL:
Raghu Samy**

CHAPTER I: DRUG SUBSTANCE

[IQA ANDA Assessment Guide Reference](#)

Drug Substance Name	Sacubitril and Valsartan
DMF Number (If Applicable)	(b)(4)
DMF Status	Adequate
DMF Holder	(b)(4)

Overall Assessment Recommendation for DS:

Adequate

Theme:

☒ N/A	☐ Other (Requires Division Director Approval)
☐ DMF	☐ Due to Consult
☐ New DS Batch	

Justification: view justification statements found at: [Justification Statements](#)

Paste appropriate justification statement(s) here or insert "N/A" if not applicable.
Other (Requires Division Director Approval)- Assessor writes justification here if "other" selected as theme.

Justification for Major from DMF review

Highlight Key Issues from Last Cycle and Their Resolution:

No Key issues with DS from last cycle review

Concise Description of Outstanding Issues:

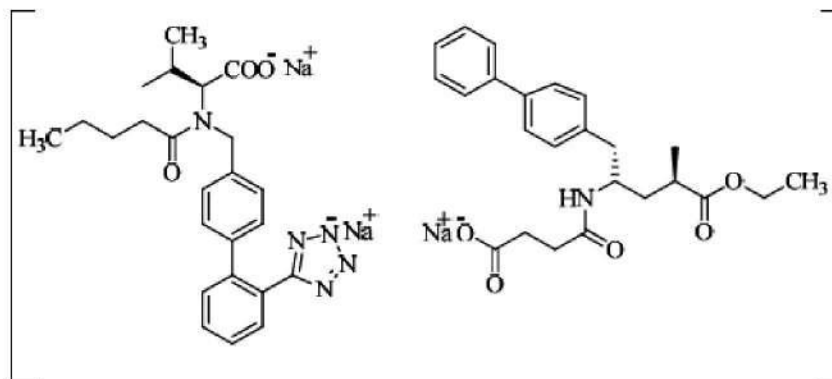
N/A - No Deficiencies with DS in the ANDA

Select Number of Approved Comparability Protocols: 00

S.1 GENERAL INFORMATION

Recommended International Nonproprietary Name	Sacubitril and Valsartan
USAN	Sacubitril and Valsartan
Chemical Name(s)	Tri sodium (4- { [(1 S,3R)-1-([1,1'-biphenyl] 4-ylmethyl)-4-ethoxy-3-methyl-4-oxobutyl]amino } -4-oxobutanoate)-(N-pentanoyl-N-{ [2'-(1H-tetrazol-1-yl-5-yl)[1,1'-biphenyl]-4-yl]methyl }-L-valinate)
CAS Number	936623-90-4
Therapeutic Category	To treat heart failure

Structure



Molecular Formula C₄₈H₅₅N₆O₈Na₃

Molecular Weight 912.96

Description White to almost white powder.

(b)(4)

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INFORMATION HAS BEEN WITHHELD IN ITS ENTIRETY IN ACCORDANCE WITH THE FOLLOWING EXEMPTIONS(S):

(b) (4)

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DRUG SUBSTANCE LIST OF DEFICIENCIES:

N/A

CHAPTER II: DRUG PRODUCT

[IQA ANDA Assessment Guide Reference](#)

Overall Assessment Recommendation:

Adequate

Theme:

☒ N/A	☐ Unacceptable Analytical Methods
☐ Unqualified Impurity	☐ Application Quality
☐ New DP Batch	☐ Pharmaceutical Equivalence
☐ Product Design	☐ Product Safety
☐ Failing Stability Data	☐ Other (Requires Division Director Approval)
☐ Application Completeness	☐ Due to Consult

Justification: view justification statements found at: [Justification Statements](#)

Paste appropriate justification statement(s) here or insert "N/A" if not applicable.
Other (Requires Division Director Approval)- Assessor writes justification here if "other" selected as theme.

Assessment Summary:

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking After Assessment Cycle #	Comments

Note: This table will be updated in Executive Summary at time of approval.

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Concise Description of Outstanding Issues (List Bullet Points with Key Information and Update as Needed): N/A

Select Number of Approved Comparability Protocols: 0

List Current Quality Endorsement Status:

- USP monograph for Drug Product and compliance (current USP) – status: not USP
- Dissolution status: dissolution method and specifications are finalized with Biopharmaceutics.
- Elemental impurity compliance with ICH Q3D – status: adequate

- Number of Comparability protocols included: 0

P.1 DESCRIPTION AND COMPOSITION

The quantitative composition and function of each excipient in the drug product is listed.

Ingredients	Functions	24 mg/ 26 mg (mg/tablet)	% w/w	49 mg/ 51 mg (mg/tablet)	% w/w	97 mg/ 103 mg (mg/tablet)	% w/w	Maximum Levels (dosage per unit) (mg)	IIG Limit for Oral Route of Administration (mg)								
(b)(4)																	
Sacubitril and Valsartan**	Active ingredient	(b)(4)															
Microcrystalline Cellulose**	(b)(4)																
(b)(4) USP-NF																	
Crospovidone																	
(b)(4) USP-NF																	
Croscarmellose Sodium																	
(b)(4) USP-NF																	
Colloidal Silicon Dioxide																	
(b)(4) USP-NF																	
Talc (b)(4) USP	(b)(4)																
Magnesium Stearate (b)(4)																	
(b)(4) USP-NF																	
(b)(4)																	
(b)(4)	(b)(4)	(b)(4)															
(b)(4)																	
(b)(4)																	
(b)(4)																	
(b)(4)																	
(b)(4)																	
Hypromellose	(b)(4)	(b)(4)															
Titanium Dioxide																	
Macrogol (b)(4)																	
(b)(4)																	
Black Iron Oxide																	
(b)(4)	(b)(4)	(b)(4)															
(b)(4)																	
(b)(4)																	
(b)(4)	(b)(4)	(b)(4)															
Iron Oxide Yellow																	
(b)(4)																	
(b)(4)																	
(b)(4)																	

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Methods Validation or Verification Package

Assessment:

Adequate

Comparability Protocols

Assessment:

N/A

Choose an item.

Lifecycle Management Considerations

DRUG PRODUCT LIST OF DEFICIENCIES)

N/A

CHAPTER III: ENVIRONMENTAL

R REGIONAL INFORMATION

Environmental

Assessment:

Adequate

CHAPTER IV: LABELING

R REGIONAL INFORMATION

1.14 Labeling

Labeling & Prescribing Information

DESCRIPTION (Rx insert or Active Ingredient(s), and Inactive Ingredients in DRUG FACTS for OTC):

Is the information accurate? ☒ Yes ☐ No

If "No," explain.

Is the drug product subject of a USP monograph? ☐ Yes ☒ No

If "Yes," does labeling have accurate USP statement in the DESCRIPTION (for Rx) or Other Information section of DRUG FACTS (for OTC)?

☐ Yes ☐ No ☐ Statement not needed

If NO, what is/are the needed statement(s)? _____

HOW SUPPLIED section (Rx insert) or Storage (in DRUG FACTS for OTC)

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Is tamper evident feature provided in the container/closure for the OTC products or Controlled Substance (CII – CIV) products? ☐ Yes ☐ No
☒ N/A (NOT OTC or Controlled Substance)

If "No," explain.

For solid oral drug products, only: drug product length(s) of commercial batch(es):

ANDA Strength	Length (MM)	Imprint Code
24 mg/ 26 mg	10.00 x 4.00	one side debossed with 'M' and other side debossed with 'S1'
49 mg/ 51 mg	13.00 x 5.10	one side debossed with 'M' and other side debossed with 'S2'
97 mg/ 103 mg	15.00 x 5.90	one side debossed with 'M' and other side debossed with 'S3'

Send issue to the Labeling assessor through the Platform with a list of quality-related labeling deficiencies and also record reference number or link for all the issues:

Issue Description	Issue Reference Number or Link

LABELING LIST OF DEFICIENCIES

N/A

ATTACHMENT II: List of All Deficiencies

N/A



Behnam
Abdolalizadeh

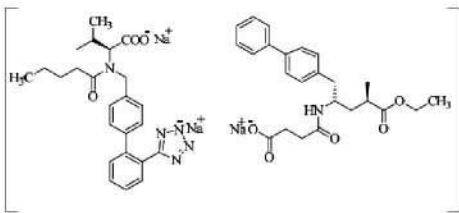
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Date: 8/09/2023 05:52:57AM
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Mayra
Pineiro Sanchez

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MANUFACTURING INTEGRATED ASSESSMENT

Application ID	ANDA 213748
Drug Product Name	Sacubitril and Valsartan Tablets  CAS #: 936623-90-4 Molecular Formula: C ₄₈ H ₅₅ N ₆ O ₈ Na ₃ Molecular Weight: 912.96 g/mol Prioritization Factor: First Generic - Granted
Strengths	24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg
Dosage Form	Tablet
Administration Route	Oral
Indication	Sacubitril and valsartan tablet is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (b)(4) and reduced ejection fraction.
Applicant Name	MSN Laboratories Private Limited
RLD Number	N207620 ENTRESTO

Reviewer's Note:

Blue font refers to the current Amendment-19 (SD#19 received 05/02/2024)/review cycle

Black font refers to the previous review cycles up to SD#14

I. Manufacturing Summary

Facility Assessment Recommendation: Adequate

Process Assessment Recommendation: Adequate

Assessment Summary:

(b)(4)

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(b)(4)

Ingredients	Functions	24 mg/ 26 mg (mg/tablet)	49 mg/ 51 mg (mg/tablet)	97 mg/ 103 mg (mg/tablet)
Intrgranular				
Sacubitril and Valsartan	API			
Microcrystalline Cellulose USP-NF#				
Crosopovidone USP-NF				
Croscarmellose Sodium SP-NF				
Colloidal Silicon Dioxide USP-NF				
Talc USP				
Magnesium Stearate USP-NF				
(b)(4)		(b)(4)		
(b)(4)				
Total tablet weight		103,000	206,000	412,000

Page 8 of 40

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(b) (4)

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None

VI. Signature Block

Round#	Primary Name	Secondary & Other Names	Date of Completion	Assessment Outcome	Facility OMIR
1	Jingbo Xiao 09/03/2019 11/22/2019 12/16/2019	Vaikunth S. Prabhu 09/05/2019 12/12/2019 12/17/2019	12/17/2019	IR	TBD
2	Jingbo Xiao 03/04/2020 04/07/2020 05/27/2020	Vaikunth S. Prabhu 03/19/2020 04/07/2020 05/27/2020	5/27/2020	CR Major	Withheld
3	Amit Kokate 1/25/2021	Jean Tang 2/1/2021	3/15/2021	CR Minor	Approve
4	Amit Kokate	Jean Tang	3/29/2022	Adequate	Approve
5	Amit Kokate	Jean Tang	2/6/2024	CR Major	Withheld
6	Amit Kokate 05/22/2024	Vaikunth Prabhu 05/30/2024	6/7/2024	Adequate	Approve



Amit
Kokate

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Vaikunth
Prabhu

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BIOPHARMACEUTICS ANDA REVIEW	
Application No.	ANDA 213748-ORIG-1
Applicant	MSN Laboratories Private Ltd.
Product Name/Strength	Sacubitril/Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg
Dosage Form/ Route of Administration:	Tablets/Oral
Indication	(b)(4)
Submission Date(s)	07/07/2019 – Original Submission 02/ 27/2020 – IR Response
RLD/RS	ENTRESTO® Tablets, 24mg/26mg,49mg/51mg & 97mg/103mg (NDA# 207620)
Primary Reviewer	Mathew John, Ph.D.
Secondary Reviewer	Om Anand, Ph.D.
Recommendation	Inadequate-Minor

Executive Summary: This Biopharmaceutics Review evaluates data supporting the adequacy of the proposed dissolution method and acceptance criteria for the proposed drug product.

The proposed drug product, Sacubitril/Valsartan Tablets, (b)(4), sacubitril and valsartan.

The Applicant originally proposed to use (b)(4)

(b)(4)

(b)(4) In the Original submission, the Applicant did not provide adequate data demonstrating the suitability of the originally proposed dissolution method (b)(4)

(b)(4)

In a response (dated 02/27/2020,) to IRs, the Applicant revised the dissolution method, (b)(4)

(b)(4)

¹ [FDA Recommended Dissolution Methods](#)

² [\\cdsesub1\evsprod\anda213748\0005\m2\27-clin-sum\pivotal-cdp-report.pdf](#)

drug product. The updated dissolution method and acceptance criterion submitted by the Applicant are tabulated in Table 1 below.

Table 1: Updated dissolution method and acceptance criterion proposed by the Applicant

Method Source	USP Apparatus	Speed (RPMs)	Medium	Volume/Temp (mL/°C)	Proposed Acceptance Criterion
(b)(4)					

The newly proposed dissolution method is acceptable. However, the proposed acceptance criterion is and not acceptable, therefore an IR will be sent to revise the dissolution acceptance criteria to NLT % (Q) in 20 minutes” [for both sacubitril and valsartan] for all strengths of the drug product.

Biopharmaceutics Recommendation: The Biopharmaceutics recommendation for ANDA 213748 for the proposed Sacubitril/Valsartan Tablets, is **pending** due to the outstanding response to the Information Request (IR) comment regarding the dissolution acceptance criterion.

Reviewer's Assessment

1. **Solubility:** (b)(4)

(b)(4)

2. **Formulation:** (b)(4)

(b)(4)

3. **Bioequivalence and PK Characteristics of the drugs:** T_{max} for sacubitril, LBQ657 (active metabolite of sacubitril), and valsartan are 0.5 hours, 2 hours, and 1.5 hours, respectively. The oral absolute bioavailability of sacubitril is estimated to be $\geq 60\%$. [Ref. Labeling]. The Applicant performed in-vivo bioequivalence studies using the proposed test and the RS products. The Applicant submitted bioequivalence study results were evaluated by the Division of Bioequivalence / OGD and was deemed inadequate⁵.

4. **Dissolution Method:** In the original submission, the Applicant used the dissolution method

(b)(4)

In the response to the IRs⁶, the Applicant accepted FDA's recommendation

(b)(4)

³ \\cdsesub1\evsprod\ANDA213748\0000\m3\32-body-data\32s-drug-sub\sacu-vals-msn-life-sciences-pvt-ltd\32s1-gen-info

⁴ \\cdsesub1\evsprod\anda213748\0000\m2\23-qos\qos-ds-word.doc

⁵ <https://panorama.fda.gov/document/preview?versionID=5df7d772007be5324bcd0016b3019064&ID=5de99fbb002c8bc85574b04e53bbcd21>

⁶ \\cdsesub1\evsprod\anda213748\0005\m1\us\1-2-cover-letters\response-to-drl-0005.pdf

⁷ \\cdsesub1\evsprod\anda213748\0005\m2\27-clin-sum\pivotal-cdp-report.pdf

(b)(4) Therefore, based on the totality of the data and justifications provided by the Applicant, the newly proposed dissolution method (Basket/75 rpm) is acceptable.

- 5. Dissolution Acceptance Criterion:** Using the new dissolution method, the dissolution data of all batches of both sacubitril and valsartan in 24 mg/26 mg and 49 mg/51 mg Tablet strengths show a (b)(4) % in (b)(4). The dissolution data for all batches of 97/103 mg Tablet strength exhibit a (b)(4) % in 20 minutes⁸. The Applicant proposed acceptance criterion is (b)(4) and therefore an IR will be sent to (b)(4) the dissolution acceptance criteria as NLT - % (Q) in 20 minutes” [for both sacubitril and valsartan] for all strengths of the drug product.

- 6. Dissolution Risk/Mitigation Assessment:** Biopharmaceutics/dissolution risk is relatively high because (b)(4). The dissolution method and acceptance criterion are set appropriately to mitigate the risk of the change in the drug product performance.

Additional Note: (b)(4)

(b)(4)

(b)(4) the Applicant proposed dissolution method using USP Type-I basket method at rotational speed of 75 rpm. This new method was found to be acceptable for the NDA and therefore, i) due to the limitations of the original method; and ii) due to the change in the dissolution method followed by the NDA; the FDA dissolution database was updated with the new dissolution method [900 mL of Phosphate Buffer, pH 6.8 using USP apparatus 1 (basket) at 75 rpm].

⁸ <\\cdsesub1\evsprod\anda213748\0005\m2\27-clin-sum\pivotal-cdp-report.pdf>

LIST OF COMMENTS FOR THE INFORMATION REQUEST # 2

Based on the provided information and data, the proposed dissolution method [USP 1 (basket) at 75 rpm/900 mL of pH 6.8 phosphate buffer] is deemed adequate for quality control testing of the proposed drug product. However, the provided dissolution data support a dissolution acceptance criterion and therefore the proposed acceptance criterion is not acceptable. Implement the following dissolution acceptance criterion for all strengths of your proposed product, Sacubitril and Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg and 97/103 mg:

“NLT % (Q) in 20 minutes” [for both sacubitril and valsartan]

Update your drug product release and stability specifications accordingly. In addition, please be advised, that all proposed exhibit batches are expected to meet these revised dissolution specifications in your stability program through your proposed expiry period. If dissolution failures are observed on stability, these should be described. Discuss any corrective actions to avert such dissolution failures and provide data from a new batch to demonstrate correction of the issue, if needed.

APPENDIX I

Information Request [dated 12/23/2019] and Response [dated 02/27/2020]

1. The proposed dissolution method [redacted] (b)(4) is not acceptable at this stage because [redacted] (b)(4). [redacted] (b)(4). [redacted] (b)(4). [redacted] (b)(4).

The limited data/information provided are not adequate to demonstrate the suitability/discriminating ability of the proposed dissolution method for your proposed drug product. Please note that the discriminating ability of the dissolution method should be investigated towards the critical material attributes (CMAs), critical process parameters (CPPs) and critical formulation variables (CFVs). In your response, justify the selection of the selected attributes /variables and their levels for demonstrating the discriminating ability of the proposed dissolution method. Described below are our recommendations with respect to proper investigation for the discriminating ability of the proposed dissolution method:

- i. Provide a list of CMAs, CPPs and CFVs affecting the dissolution and establish that your method is discriminating towards those CMAs (including the drug substance particle size distribution), CPPs and CFVs which affect dissolution. In general, the testing conducted to demonstrate the discriminating ability of the dissolution method should compare the dissolution profiles of the proposed drug product(target) and the formulations/product that are intentionally manufactured with meaningful variations, i.e., aberrant formulations and manufacturing conditions with $\pm 10\text{-}20\%$ change to the specification-ranges of these variables for the most relevant CMA's and CPPs.
- ii. In addition, if available, data can be submitted showing that the selected dissolution method is able to reject batches that are not bioequivalent. Supportive dissolution data may also be submitted showing that the selected dissolution method can detect the change(s) in the drug product occurring during the accelerated and stressed conditions.
- iii. Provide i) the manufacturing date, storage conditions and the age of the batches used in the above studies, ii) the number of dosage units used to generate the dissolution data, iii) complete dissolution data (individual, mean, cv%) in tabulated format, and iv) graphic presentation for the mean dissolution data for each table.

The adequacy of the proposed dissolution acceptance criterion will be determined after the accessing the above requested information.

The limited in dissolution data demonstrate that the dissolution of some units of the test product remains incomplete using your proposed method, for example some units of Batch # DT1812065 dissolved [redacted] (b)(4) % and a mean of [redacted] (b)(4) % at [redacted] (b)(4). Explain the root cause of the incomplete dissolution of the proposed drug product using your proposed method. Support your explanation with appropriate data. Submit dissolution

[USP apparatus 2(paddle) at 50 rpm] profile data using the currently available long-term stability batches. Indicate the age of the batch at the time of dissolution testing.

2. Note that the FDA dissolution database[https://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_SearchResults.cfm] has been updated with a new dissolution method [900 mL of Phosphate Buffer, pH 6.8 using USP apparatus 1 (basket) at 75 rpm]. Please submit dissolution data [(N=12, individual, mean, cv%)] for all your exhibits batches using this method. (b)(4)
- (b)(4), the dissolution of your proposed drug product remains incomplete or you notice cone formation, then you may consider this new FDA method for the quality control testing of your proposed drug product. If you choose to do so, the please submit the information/data showing the suitability/discriminating ability of the proposed dissolution method for your proposed drug product, as per above recommendations regarding the demonstration of the suitability/discriminating ability.

Applicant's Response [dated 02/27/2020]:

The Applicant's detailed response is available at the following link⁹:

The Applicant adopted the dissolution method currently available in the FDA dissolution data base for this drug product as tabulated in Table 1. The Applicant has also submitted the comparative dissolution profiles in section 2.7 of the submission as per the current dissolution method. The Applicant has also studied the discriminative ability of the method (b)(4)

(b)(4)

Reviewer's Assessment of the response: The Applicant proposed new dissolution method for the proposed drug product is acceptable. However, the proposed dissolution acceptance criterion of (b)(4) for all strengths of both Sacubitril and Valsartan is (b)(4) and therefore, the Applicant will be recommended to implement a (b)(4) dissolution acceptance criterion (Please see IR # 2).

⁹ <\\cdsesub1\evsprod\anda213748\0005\m1\us\1-2-cover-letters\response-to-drl-0005.pdf>

APPENDIX II

Dissolution Profile Data

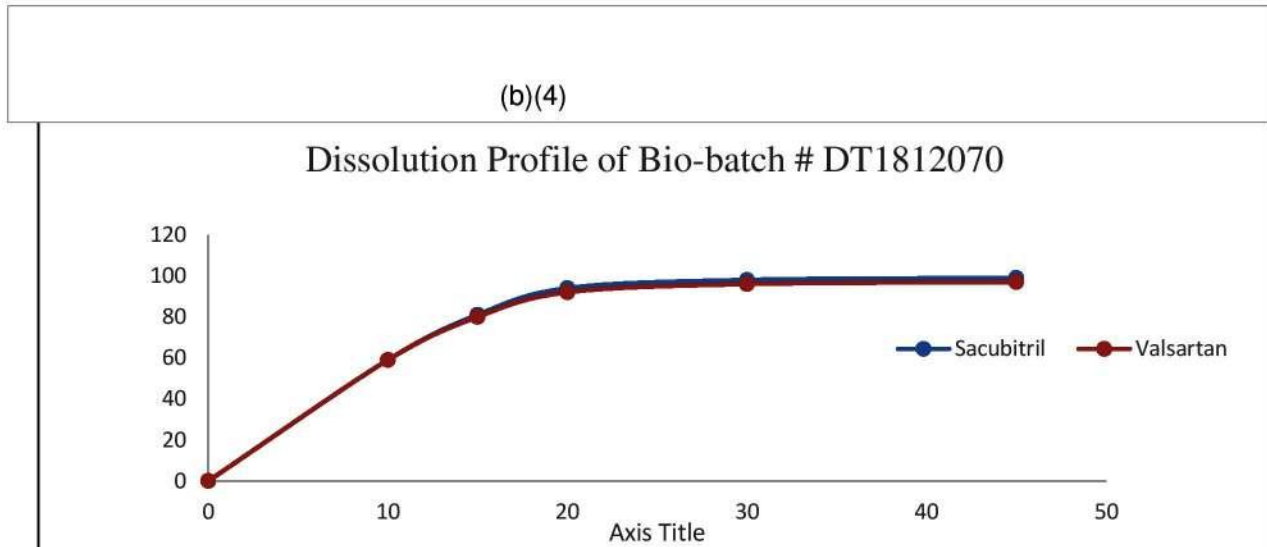
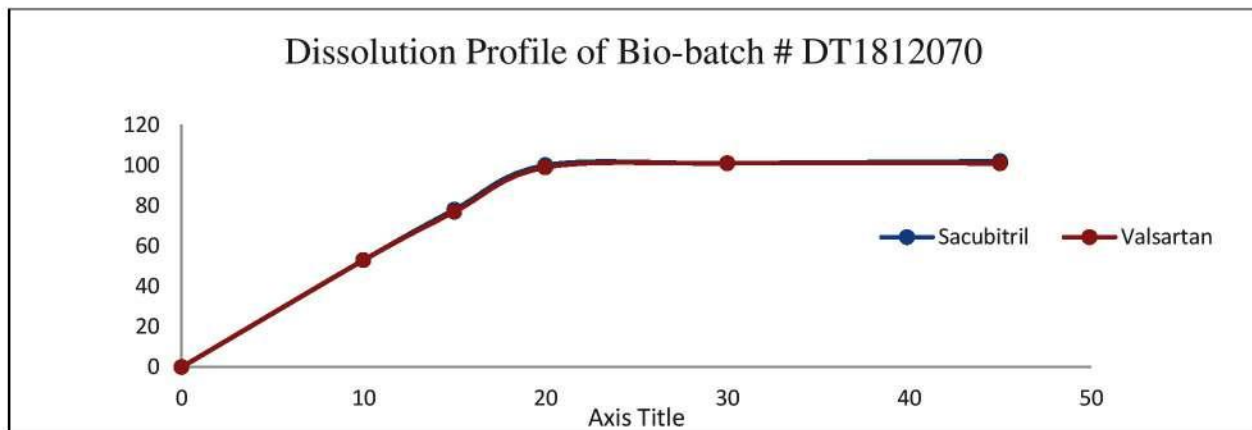


Figure 2: In vitro dissolution profile of drug product strength 97 mg / 103 mg biobatch # DT1812070 using the current method in the FDA dissolution database (USP Apparatus 1/ 75 rpm)¹¹



¹⁰ <\\cdsesub1\evsprod\anda213748\0000\m2\27-clin-sum\pivotal-biosummary-tables-pdf.pdf>

¹¹ <\\cdsesub1\evsprod\anda213748\0005\m2\27-clin-sum\pivotal-cdp-report.pdf>



Using the newly proposed dissolution method, the biobatch and all the exhibit batches shows % drug release by 20 minutes. The submitted dissolution data supports a dissolution acceptance criterion (refer IR #2) and will be communicated to the Applicant.



Om
Anand

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Mathew
John

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Date: 4/23/2020 09:59:31AM
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BIOPHARMACEUTICS ASSESSMENT	
Application No.	ANDA-213748-ORIG-1-AMEND-8
Submission Type	Solicited Major Amendment
Applicant	MSN LABORATORIES PRIVATE LIMITED
Product Name	Sacubitril and Valsartan Tablets
Dosage Form/Strengths	IR Tablet; 24 mg/26 mg, 49 mg/51 mg and 97mg/103 mg
Route of Administration	Oral
Indication	(b)(4)
Submission Date	8/19/20
Goal Date	4/18/2021
Primary Reviewer	Ho-Pi Lin, Ph.D.
Secondary Reviewer	N/A
Recommendation	ADEQUATE

EXECUTIVE SUMMARY

Background:

This amendment (#8) was submitted in response to the complete response (CR) letter issued on 6/8/2020 for the original submission. Previous assessment was documented in Panorama.¹ The assessment concluded inadequate was due to inadequate dissolution acceptance criterion.

Previous CR Comments

Based on the provided information and data, the proposed dissolution method [USP 1 (basket) at 75 rpm/900 mL of pH 6.8 phosphate buffer] is deemed adequate for quality control testing of the proposed drug product. However, the provided dissolution data support a dissolution acceptance criterion and therefore the proposed acceptance criterion is not acceptable. Implement the following dissolution acceptance criterion for all strengths of your proposed product, Sacubitril and Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg and 97/103 mg:
“NLT % (Q) in 20 minutes” [for both sacubitril and valsartan]

¹

<https://panorama.fda.gov/internal/document/preview?versionID=5eac76cf01b56ba5c2cd6ace37d442ec&ID=5dfd0f2d0014e7e092033c3228682dac>

Update your drug product release and stability specifications accordingly. In addition, please be advised, that all proposed exhibit batches are expected to meet these revised dissolution specifications in your stability program through your proposed expiry period. If dissolution failures are observed on stability, these should be described. Discuss any corrective actions to avert such dissolution failures and provide data from a new batch to demonstrate correction of the issue, if needed.

Biopharmaceutics Assessment:

The Applicant accepted² and implemented³ the recommended criterion. The response is acceptable.

Recommendation:

This ANDA 213748 is recommended for approval from a biopharmaceutics perspective.

Approved disintegration method and acceptance criterion/criteria:

USP Apparatus	Speed	Medium/Temperature	Acceptance criterion(a)
I (Basket)	75 rpm	pH 6.8 phosphate buffer/37°C 900 ml	Q= % in 20 minutes (Sacubitril & Valsartan)

² Page 5 in <file:///C:/cdsesub1/evsprod/ANDA213748/0007/m1/us/1-2-cover-letters/response-to-crl-0007.pdf>

³ <file:///C:/cdsesub1/evsprod/ANDA213748/0007/m3/32-body-data/32p-drug-prod/sac-vlsrtn-tab-msn-lab/32p5-contr-drug-prod/32p51-spec/specifications.pdf>



Ho-Pi
Lin

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Pineiro Sanchez

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ANDA Executive Summary

1. Application/Product Information

ANDA Number.	213748		
Review Cycle #	05		
Applicant Name	MSN Laboratories Private Limited		
Drug Product Name	Sacubitril and Valsartan		
Dosage Form. (click (+) for more than one)	Tablet		
Proposed Strength(s)	24 mg/26 mg, 49 mg /51 mg and 97 mg/103 mg		
Route of Administration (click (+) for more than one)	Oral		
Maximum Daily Dose	sacubitril 97 mg and valsartan 103 mg x 2/day		
Rx/OTC Dispensed	Rx		
Proposed Indication	Sacubitril and valsartan tablet is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (b)(6) and reduced ejection fraction.		
Drug Product Description	Refer to 3.2.P.1		
Co-packaged product information	N/A		
Device information, if any:	N/A		
Storage Temperature/ Conditions	Store at 25°C (77°F), excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from moisture.		
Review Team	Discipline	Primary	Secondary
	<i>Drug Substance</i>	Behnam Abdolalizadeh	Mayra Pineiro-Sanchez

	<i>Drug Product/ Labeling</i>	Behnam Abdolalizadeh	Mayra Pineiro-Sanchez
	<i>Manufacturing</i>	Amit Kokate	Jean Tang R05: Vaikunth Prabhu
	<i>Biopharmaceutics</i>	Ho-Pi Lin	N/A
	<i>Microbiology</i>	N/A	N/A
	<i>Other (specify):</i>	N/A	N/A
	<i>RBPM</i>	Candice Cottle-Delisle R05: Jennifer Nguyen	
	<i>ATL</i>	Mayra Pineiro-Sanchez	
Consults	Discipline Consulted	Recommendation	Date

2. Submission Document(s) Reviewed

Submission(s) Assessed	Documents Date	Disciplines Affected
Original/Initial Submission	07/08/2019	All
Labeling-response to DRL	10/30/2019	Labeling
Quality/Response to Discipline Review Letter	02/27/2020	Quality
Resubmission/After Action- Complete Response	08/19/2020	Quality
Quality/Response To Information Request	08/28/2020	Quality
CR Response	02/09/2022	Quality
IR response	02/23/2022	Quality
CR Response	12/27/2022	Quality/Labeling
Quality/Response To Information Request	07/06/2023	Quality
CR Response	05/02/2024	Quality/Labeling

3. Related/Supporting Documents

a. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Assessor/ Comments
(b)(4)	II	(b)(4)	Sacubitril and Valsartan	Adequate	07/12/2023	R05
	II		(b)(4)	Adequate	02/09/2022	
	II			Adequate	04/05/2022	
	IV					
	IV					
	IV					
	III					Refer to 3.2.P.7
	(b)(4)					

b. Other Documents: *IND, RLD, RS, Approved ANDA*

Document	Application Number	Description
RLD	NDA 207620	ENTRESTO®

4. Final Overall recommendation – Approval

Deficiencies (if applicable):

Overall Quality Deficiencies - Optional (*Deficiencies that affect multiple sub-disciplines; for subheadings use the format shown, for all deficiencies.*)

Drug Substance Deficiencies

Drug Product Deficiencies

Labeling Deficiencies (*Please contact OGD if you identify any Labeling deficiencies with your comments*)

Manufacturing Deficiencies

Biopharmaceutics Deficiencies

Microbiology Deficiencies

Other Deficiencies (Specify discipline, such as Environmental. For consults such as Biostatistics, PharmTox, CDRH, Clinical, etc., include consult type and specify Quality discipline – example: **Pharm/Tox consult for Drug Product**)

Additional Comments:

In addition to responding to the deficiencies presented above, please note and acknowledge the following comment(s) in your response:

5. Basis for Recommendation

a. Summary of Rationale for Recommendation:

The ANDA submitted on the basis of NDA 207620 (RLD), ENTRESTO includes sufficient information to assure the identity, strength, purity, and quality of the drug product during the expiration dating period of 24 months. The applicant has provided acceptable raw material, in-process, and finished product controls and established an adequate dissolution specification (method and acceptance criteria) for routine quality control of the finished product. The overall facility assessment recommends approval and the labels have adequate quality information. Applicant states categorical exclusion from the requirement of Environmental Impact Analysis per 21 CFR 25.31. Therefore, from the quality perspective, this ANDA is recommended for approval.

(b)(4)

b. Recommendation by Subdiscipline:

Drug Substance: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view [Justification Statements](#))

1.

Drug Product: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view [Justification Statements](#))

1.

Quality Labeling: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view [Justification Statements](#))

1.

Manufacturing: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view [Justification Statements](#))

1.

Biopharmaceutics: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view [Justification Statements](#))

1.

Microbiology: N/A

Provide justification(s) (for major deficiencies only):
(Click link to view [Justification Statements](#))

1.

Environmental: N/A

Provide justification(s) (for major deficiencies only):
(Click link to view [Justification Statements](#))

1.

6. Life-Cycle Considerations

**Established Conditions per ICH Q12: No
Comments:**

**Comparability Protocols (PACMP): No
Comments:**

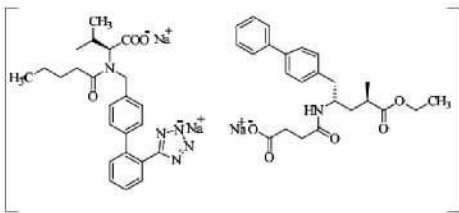
Additional Comments:



Mayra
Pineiro Sanchez

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Date: 6/11/2024 04:47:59PM
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MANUFACTURING INTEGRATED ASSESSMENT

Application ID	ANDA 213748
Drug Product Name	Sacubitril and Valsartan Tablets  CAS #: 936623-90-4 Molecular Formula: C ₄₈ H ₅₅ N ₆ O ₈ Na ₃ Molecular Weight: 912.96 g/mol Prioritization Factor: First Generic - Granted
Strengths	24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg
Dosage Form	Tablet
Administration Route	Oral
Indication	Sacubitril and valsartan tablet is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (b)(4) and reduced ejection fraction.
Applicant Name	MSN Laboratories Private Limited
RLD Number	N207620 ENTRESTO

Reviewer's Note:

Blue font refers to the current Amendment-19 (SD#19 received 05/02/2024)/review cycle

Black font refers to the previous review cycles up to SD#14

I. Manufacturing Summary

Facility Assessment Recommendation: Adequate

Process Assessment Recommendation: Adequate

Assessment Summary:

(b)(4)

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IT IS NOT REASONABLE TO SEGREGATE MEANINGFUL PORTIONS OF THE RECORD FOR RELEASE.

INFORMATION HAS BEEN WITHHELD IN ITS ENTIRETY IN ACCORDANCE WITH THE FOLLOWING EXEMPTIONS(S):

(b) (4)

5 U.S.C. 552 (b) (4) - trade secrets and commercial or financial information obtained from a person and privileged or confidential.

II.

(b)(4)

Manufacturing

1. Batch Formula

Ingredients	Functions	24 mg/ 26 mg (mg/tablet)	49 mg/ 51 mg (mg/tablet)	97 mg/ 103 mg (mg/tablet)	(b)(4)																																										
<table border="1"> <tr> <td colspan="2">Sacubitril and Valsartan</td> <td colspan="4">API</td> </tr> <tr> <td>Microcrystalline Cellulose</td> <td>(b)(4)</td> <td colspan="4">USP-NF#</td> </tr> <tr> <td>Croscopovidone</td> <td>(b)(4)</td> <td colspan="4">USP-NF#</td> </tr> <tr> <td>Croscarmellose Sodium</td> <td>(b)(4)</td> <td colspan="4">SP-NF#</td> </tr> <tr> <td>Colloidal Silicon Dioxide</td> <td>(b)(4)</td> <td colspan="4">USP-NF#</td> </tr> <tr> <td>Talc</td> <td>(b)(4)</td> <td colspan="4">USP</td> </tr> <tr> <td>Magnesium Stearate</td> <td>(b)(4)</td> <td colspan="4">USP-NF#</td> </tr> </table>						Sacubitril and Valsartan		API				Microcrystalline Cellulose	(b)(4)	USP-NF#				Croscopovidone	(b)(4)	USP-NF#				Croscarmellose Sodium	(b)(4)	SP-NF#				Colloidal Silicon Dioxide	(b)(4)	USP-NF#				Talc	(b)(4)	USP				Magnesium Stearate	(b)(4)	USP-NF#			
Sacubitril and Valsartan		API																																													
Microcrystalline Cellulose	(b)(4)	USP-NF#																																													
Croscopovidone	(b)(4)	USP-NF#																																													
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Colloidal Silicon Dioxide	(b)(4)	USP-NF#																																													
Talc	(b)(4)	USP																																													
Magnesium Stearate	(b)(4)	USP-NF#																																													
(b)(4)	(b)(4)	(b)(4)																																													
(b)(4)	(b)(4)	(b)(4)																																													
Total tablet weight		103.000	206.000	412.000	(b)(4)																																										

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INFORMATION HAS BEEN WITHHELD IN ITS ENTIRETY IN ACCORDANCE WITH THE FOLLOWING EXEMPTIONS(S):

(b) (4)

5 U.S.C. 552 (b) (4) - trade secrets and commercial or financial information obtained from a person and privileged or confidential.

None

VI. Signature Block

Round#	Primary Name	Secondary & Other Names	Date of Completion	Assessment Outcome	Facility OMIR
1	Jingbo Xiao 09/03/2019 11/22/2019 12/16/2019	Vaikunth S. Prabhu 09/05/2019 12/12/2019 12/17/2019	12/17/2019	IR	TBD
2	Jingbo Xiao 03/04/2020 04/07/2020 05/27/2020	Vaikunth S. Prabhu 03/19/2020 04/07/2020 05/27/2020	5/27/2020	CR Major	Withheld
3	Amit Kokate 1/25/2021	Jean Tang 2/1/2021	3/15/2021	CR Minor	Approve
4	Amit Kokate	Jean Tang	3/29/2022	Adequate	Approve
5	Amit Kokate	Jean Tang	2/6/2024	CR Major	Withheld
6	Amit Kokate 05/22/2024	Vaikunth Prabhu 05/30/2024	6/7/2024	Adequate	Approve



Amit
Kokate

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Vaikunth
Prabhu

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Date: 6/07/2024 10:13:32AM
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MEMORANDUM T O FILE- Facility Major to Minor Reclassification Request
OPQ/OPMA Assessors: Amit Kokate, Vaikunth Prabhu

ANDA No./Drug Name	ANDA-213748-ORIG-1-AMEND-19 Sacubitril and Valsartan Tablets, 24 mg/26 mg, 49 mg /51 mg, and 97 mg/103 mg
Applicant	MSN Laboratories Private Limited
Decision	GRANTED
Date	5/22/2024

RESPONSE TO BE COMMUNICATED WITH THE APPLICANT:

Reason (s) for Denial: N/A

(b)(4)

Therefore, this Facility Major to Minor Reclassification Request is recommended to be granted from OPMA's perspective.



Amit
Kokate

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Date: 5/31/2024 11:08:47AM
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Vaikunth
Prabhu

Digitally signed by Vaikunth Prabhu
Date: 5/31/2024 12:26:36PM
GUID: 508da70600028a6e0679d7b5b0fd3db3

ANDA Executive Summary

1. Application/Product Information

ANDA Number.	213748		
Review Cycle #	04		
Applicant Name	MSN Laboratories Private Limited		
Drug Product Name	Sacubitril and Valsartan		
Dosage Form. (click (+) for more than one)	Tablet		
Proposed Strength(s)	24 mg/26 mg, 49 mg /51 mg and 97 mg/103 mg		
Route of Administration (click (+) for more than one)	Oral		
Maximum Daily Dose	sacubitril 97 mg and valsartan 103 mg x 2/day		
Rx/OTC Dispensed	Rx		
Proposed Indication	Sacubitril and valsartan tablet is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (b)(4) and reduced ejection fraction.		
Drug Product Description	Refer to 3.2.P.1		
Co-packaged product information	N/A		
Device information, if any:	N/A		
Storage Temperature/ Conditions	Store at 25°C (77°F), excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from moisture.		
Review Team	Discipline	Primary	Secondary
	<i>Drug Substance</i>	Behnam Abdolalizadeh	Mayra Pineiro-Sanchez

	<i>Drug Product/ Labeling</i>	Behnam Abdolalizadeh	Mayra Pineiro-Sanchez
	<i>Manufacturing</i>	Amit Kokate	Jean Tang
	<i>Biopharmaceutics</i>	Ho-Pi Lin	N/A
	<i>Microbiology</i>	N/A	N/A
	<i>Other (specify):</i>	N/A	N/A
	<i>RBPM</i>	Candice Cottle-Delisle	
	<i>ATL</i>	Mayra Pineiro-Sanchez	
Consults	Discipline Consulted	Recommendation	Date

2. Submission Document(s) Reviewed

Submission(s) Assessed	Documents Date	Disciplines Affected
Original/Initial Submission	07/07/2019	All
Labeling-response to DRL	10/30/2019	Labeling
Quality/Response to Discipline Review Letter	2/27/2020	Quality
Resubmission/After Action- Complete Response	08/19/2020	Quality
Quality/Response To Information Request	08/28/2020	Quality
CR Response	02/09/2022	Quality
IR response	02/23/2022	Quality
CR Response	12/27/2022	Quality/Labeling
Quality/Response To Information Request	07/06/2023	Quality

3. Related/Supporting Documents

a. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Assessor/ Comments
(b)(4)	II	(b)(4)	Sacubitril and Valsartan	Adequate	07/12/2023	R05
	II		(b)(4)	Adequate	02/09/2022	
	II			Adequate	04/05/2022	
	IV					
	IV					
	IV					
	III					Refer to 3.2.P.7

b. Other Documents: IND, RLD, RS, Approved ANDA

Document	Application Number	Description
RLD	NDA 207620	ENTRESTO®

4. Final Overall recommendation – Complete Response-Major-Facilities Only

Deficiencies (if applicable):

Overall Quality Deficiencies - Optional (*Deficiencies that affect multiple sub-disciplines; for subheadings use the format shown, for all deficiencies.*)

1.

Drug Substance Deficiencies

1.

Drug Product Deficiencies

1.

Labeling Deficiencies *(Please contact OGD if you identify any Labeling deficiencies with your comments)*

1.

Manufacturing Deficiencies

(b)(4)

Biopharmaceutics Deficiencies

1.

Microbiology Deficiencies

1.

Other Deficiencies *(Specify discipline, such as Environmental. For consults such as Biostatistics, PharmTox, CDRH, Clinical, etc., include consult type and specify Quality discipline – example: Pharm/Tox consult for Drug Product)*

1.

Additional Comments:

In addition to responding to the deficiencies presented above, please note and acknowledge the following comment(s) in your response:

5. Basis for Recommendation

a. Summary of Rationale for Recommendation:

The ANDA submitted on the basis of NDA 207620 (RLD), ENTRESTO® is not recommended for approval. A MAJOR CR is recommended due to facility

(b)(4)

(b)(4)

b. Recommendation by Subdiscipline:

Drug Substance: ADEQUATE

Provide justification(s) (for major deficiencies only):

(Click link to view [Justification Statements](#))

1.

Drug Product: ADEQUATE

Provide justification(s) (for major deficiencies only):

(Click link to view [Justification Statements](#))

1.

Quality Labeling: ADEQUATE

Provide justification(s) (for major deficiencies only):

(Click link to view [Justification Statements](#))

1.

Manufacturing: INADEQUATE-MAJOR-Facilities Only

Provide justification(s) (for major deficiencies only):

(Click link to view [Justification Statements](#))

The facilities deficiencies have been classified as MAJOR because one or more facilities were found inadequate at the time of action due to inspectional deficiencies as noted in Appendix A, Section A(6)(a) of the Guidance for Industry, ANDA Submissions - Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). Note that after the deficiencies have been purportedly resolved, FDA must assess the resolution of the cited deficiencies during the next review cycle. This assessment, upon receipt of an amendment responding to this deficiency, in FDA's judgement, will require substantial expenditure of FDA resources.

Biopharmaceutics: ADEQUATE

Provide justification(s) (for major deficiencies only):

(Click link to view [Justification Statements](#))

1.

Microbiology: N/A

Provide justification(s) (for major deficiencies only):
(Click link to view [Justification Statements](#))

1.

Environmental: N/A

Provide justification(s) (for major deficiencies only):
(Click link to view [Justification Statements](#))

1.

6. Life-Cycle Considerations

**Established Conditions per ICH Q12: No
Comments:**

**Comparability Protocols (PACMP): No
Comments:**

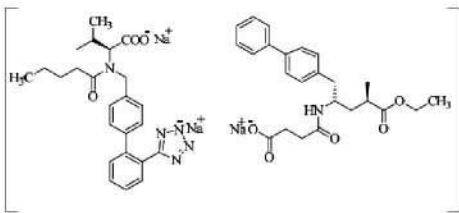
Additional Comments:



Mayra
Pineiro Sanchez

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Date: 2/14/2024 06:55:32PM
GUID: 508da702000288099b99e9faff8a6a27

MANUFACTURING INTEGRATED ASSESSMENT

Application ID	ANDA 213748
Drug Product Name	Sacubitril and Valsartan Tablets  CAS #: 936623-90-4 Molecular Formula: C ₄₈ H ₅₅ N ₆ O ₈ Na ₃ Molecular Weight: 912.96 g/mol Prioritization Factor: First Generic - Granted
Strengths	24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg
Dosage Form	Tablet
Administration Route	Oral
Indication	Sacubitril and valsartan tablet is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (b)(4) and reduced ejection fraction.
Applicant Name	MSN Laboratories Private Limited
RLD Number	N207620 ENTRESTO

Reviewer's Note:

Blue font refers to the current Amendment-14 (SD#14 received 12/27/2022)/review cycle

Black font refers to the previous review cycles up to SD#12 (received 02/09/2022)

I. Manufacturing Summary

Facility Assessment Recommendation: Inadequate - Major

THEME: Inadequate Facility - cGMP (b)(4)

JUSTIFICATION: The facilities deficiencies have been classified as MAJOR because one or more facilities were found inadequate at the time of action due to inspectional deficiencies as noted in Appendix A, Section A(6)(a) of the Guidance for Industry, ANDA Submissions - Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). Note that after the deficiencies have been purportedly resolved, FDA must assess the resolution of the cited deficiencies during the next review cycle. This assessment, upon receipt of an amendment responding to this deficiency, in FDA's judgement, will require substantial expenditure of FDA resources.

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INFORMATION HAS BEEN WITHHELD IN ITS ENTIRETY IN ACCORDANCE WITH THE FOLLOWING EXEMPTIONS(S):

(b) (4)

5 U.S.C. 552 (b) (4) - trade secrets and commercial or financial information obtained from a person and privileged or confidential.

(b)(4)

List Submissions being assessed (Table):

Document Description (SD #)	Date Received
Original Submission, Seq. 0000 (1)	07/08/2019
CMC Amendment (Response to DRL), Seq. 0005 (6)	02/27/2020
CMC Amendment (Response to CRL), Seq. 0007 (8); Amend-8	08/19/2020
CMC Amendment (Response to IR), Seq. 0008 (9)	08/28/2020
CMC Amendment (Response to CRL), Seq. 0011 (12)	02/09/2022



QUALITY ASSESSMENT



CMC Amendment (Response to IR), Seq. 0012 (13)	02/23/2022
CMC Amendment (Response to CR), Seq. 0013 (14)	12/27/2022

Note: Seq. 0001 (2), 0002 (3), 0003 (4), 0004 (5), 0006 (7), 0009 (10), 0010(11), 0014(15), 0015(16), 0016(17), 0017(18) are not CMC related submissions or do not contain OPMA related information.

Highlight Key Issues from Last Cycle and Their Resolution: See CR#1

-
-

(b)(4)

Concise Description of Outstanding Issues (List bullet points with key information and update as needed):

-

(b)(4)

List Number of Comparability Protocols: None

1. Lifecycle Management Considerations

Post-approval inspection?	No
Lifecycle considerations	No

2. Facilities Table

Facility name and address	FEI	Responsibilities and profile code(s)	Status
(b)(4)			
MSN Life sciences Private Limited Unit-II, Sy.No. 455/A,455/AA,455/E and 455/EE Chandampet (Village), Shankarampet-R (Mandal), Medak District, Telangana, INDIA, 502255	3011543392	(b)(4)	Approve - Based on PAI
MSN Laboratories Private Limited (Research & Development)	3005075182		No Evaluation Necessary

Plot No. 12, Phase-IV, Sy.No. 119 to 140, 258, 275 to 280, Industria Park, Pashamylaram (Village), Patancheru (Mandal), Sanga reddy district, Telangana, INDIA, 502307		(b)(4)	
MSN Laboratories Private Limited Sy. No. 317 & 320, 321, 322,323, 604 & 605, Rudraram (Village), Patancheru (Mandal), Sangareddy District, Telangana, India, 502329	3005254981	(b)(4)	Approve - Based on Previous History
(b)(4)			
MSN Pharmachem Private Limited Plot No.: 212/ A,B,C,D, Phase-II, IDA Pashamylaram, Pashamylaram (Village), Patancheru (Mandal), , Sangareddy District,, Telangana,, India, 502 307	3006165229	(b)(4)	Approve - Based on Previous History

Update (Amendment-8):

(b)(4)

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INFORMATION HAS BEEN WITHHELD IN ITS ENTIRETY IN ACCORDANCE WITH THE FOLLOWING EXEMPTIONS(S):

(b) (4)

5 U.S.C. 552 (b) (4) - trade secrets and commercial or financial information obtained from a person and privileged or confidential.

(b)(4)

1. Batch Formula

Ingredients		Functions	24 mg/ 26 mg (mg/tablet)	49 mg/ 51 mg (mg/tablet)	97 mg/ 103 mg (mg/tablet)	(b)(4)
Sacubitril and Valsartan		API	(b)(4)			
Microcrystalline Cellulose (NDA) USP-NF#						
Crospovidone (NDA) USP-NF						
Croscarmellose Sodium (NDA) SP-NF						
Colloidal Silicon Dioxide (NDA)						
Talc (NDA) USP						
Magnesium Stearate (NDA) USP-NF						
Total tablet weight						

(b)(4)

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Outstanding Deficiencies Collation Table

1)

(b)(4)

VI. Signature Block

Round#	Primary Name	Secondary & Other Names	Date of Completion	Assessment Outcome	Facility OMIR
1	Jingbo Xiao 09/03/2019 11/22/2019 12/16/2019	Vaikunth S. Prabhu 09/05/2019 12/12/2019 12/17/2019	12/17/2019	IR	TBD
2	Jingbo Xiao 03/04/2020 04/07/2020 05/27/2020	Vaikunth S. Prabhu 03/19/2020 04/07/2020 05/27/2020	5/27/2020	CR Major	Withheld
3	Amit Kokate 1/25/2021	Jean Tang 2/1/2021	3/15/2021	CR Minor	Approve
4	Amit Kokate	Jean Tang	3/29/2022	Adequate	Approve
5	Amit Kokate	Jean Tang	2/6/2024	CR Major	Withheld



Amit
Kokate

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Jean
Tang

Digitally signed by Jean Tang
Date: 2/07/2024 11:11:21AM
GUID: 502d1ab500002aff2e492acb1fd0d645

ANDA Executive Summary

1. Application/Product Information

ANDA Number.	213748		
Review Cycle #	04		
Applicant Name	MSN Laboratories Private Limited		
Drug Product Name	Sacubitril and Valsartan		
Dosage Form. (click (+) for more than one)	Tablet		
Proposed Strength(s)	24 mg/26 mg, 49 mg /51 mg and 97 mg/103 mg		
Route of Administration (click (+) for more than one)	Oral		
Maximum Daily Dose	sacubitril 97 mg and valsartan 103 mg x 2/day		
Rx/OTC Dispensed	Rx		
Proposed Indication	Sacubitril and valsartan tablet is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (b)(4) and reduced ejection fraction.		
Drug Product Description	Refer to 3.2.P.1		
Co-packaged product information	N/A		
Device information, if any:	N/A		
Storage Temperature/ Conditions	Store at 25°C (77°F), excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from moisture.		
Review Team	Discipline	Primary	Secondary
	<i>Drug Substance</i>	Behnam Abdolalizadeh	Mayra Pineiro-Sanchez

	<i>Drug Product/ Labeling</i>	Behnam Abdolalizadeh	Mayra Pineiro-Sanchez
	<i>Manufacturing</i>	Amit Kokate	Jean Tang
	<i>Biopharmaceutics</i>	Ho-Pi Lin	N/A
	<i>Microbiology</i>	N/A	N/A
	<i>Other (specify):</i>	N/A	N/A
	<i>RBPM</i>	Candice Cottle-Delisle	
	<i>ATL</i>	Mayra Pineiro-Sanchez	
Consults	Discipline Consulted	Recommendation	Date

2. Submission Document(s) Reviewed

Submission(s) Assessed	Documents Date	Disciplines Affected
Original/Initial Submission	07/07/2019	All
Labeling-response to DRL	10/30/2019	Labeling
Quality/Response to Discipline Review Letter	2/27/2020	Quality
Resubmission/After Action- Complete Response	08/19/2020	Quality
Quality/Response To Information Request	08/28/2020	Quality
CR Response	02/09/2022	Quality
IR response	02/23/2022	Quality
CR Response	12/27/2022	Quality/Labeling
Quality/Response To Information Request	07/06/2023	Quality

3. Related/Supporting Documents

a. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Assessor/ Comments
(b)(4)	II	(b)(4)	Sacubitril and Valsartan	Adequate	07/12/2023	R05
	II		(b)(4)	Adequate	02/09/2022	
	II			Adequate	04/05/2022	
	IV					
	IV					
	IV					
	III					Refer to 3.2.P.7

b. Other Documents: IND, RLD, RS, Approved ANDA

Document	Application Number	Description
RLD	NDA 207620	ENTRESTO®

4. Final Overall recommendation – Approval

Deficiencies (if applicable):

NONE

Overall Quality Deficiencies - Optional (*Deficiencies that affect multiple sub-disciplines; for subheadings use the format shown, for all deficiencies.*)

1.

Drug Substance Deficiencies

1.

Drug Product Deficiencies

1.

Labeling Deficiencies *(Please contact OGD if you identify any Labeling deficiencies with your comments)*

1.

Manufacturing Deficiencies

1.

Biopharmaceutics Deficiencies

1.

Microbiology Deficiencies

1.

Other Deficiencies *(Specify discipline, such as Environmental. For consults such as Biostatistics, PharmTox, CDRH, Clinical, etc., include consult type and specify Quality discipline – example: Pharm/Tox consult for Drug Product)*

1.

Additional Comments:

In addition to responding to the deficiencies presented above, please note and acknowledge the following comment(s) in your response:

5. Basis for Recommendation

a. Summary of Rationale for Recommendation:

*The ANDA submitted on the basis of NDA 207620 (RLD), ENTRESTO® includes sufficient information to assure the identity, strength, purity, and quality of the drug product during the expiration dating period of 24 months. The applicant has provided acceptable raw material, in-process, and finished product controls and established an adequate dissolution specification (method and acceptance criteria) for routine quality control of the finished product. The overall facility assessment recommends approval and the labels** have adequate quality information. Therefore, from the quality perspective, this ANDA is recommended for approval.*

(b)(4)

(b)(4)

b. Recommendation by Subdiscipline:

Drug Substance: ADEQUATE

Provide justification(s) (for major deficiencies only):

(Click link to view [Justification Statements](#))

1.

Drug Product: ADEQUATE

Provide justification(s) (for major deficiencies only):

(Click link to view [Justification Statements](#))

1.

Quality Labeling: ADEQUATE

Provide justification(s) (for major deficiencies only):

(Click link to view [Justification Statements](#))

1.

Manufacturing: ADEQUATE

Provide justification(s) (for major deficiencies only):

(Click link to view [Justification Statements](#))

1.

Biopharmaceutics: ADEQUATE

Provide justification(s) (for major deficiencies only):

(Click link to view [Justification Statements](#))

1.

Microbiology: N/A

Provide justification(s) (for major deficiencies only):

(Click link to view [Justification Statements](#))

1.

Environmental: N/A

Provide justification(s) (for major deficiencies only):

(Click link to view [Justification Statements](#))

1.

6. Life-Cycle Considerations

Established Conditions per ICH Q12: No

Comments:

Comparability Protocols (PACMP): No

Comments:

Additional Comments:

OGD Policy Alert: **YES** (05SEP2023)

FDA-2021-P-1286 (NDA 207620)

Entresto sacubitril; valsartan tablets

Petition requests that the FDA refrain from approving an ANDA relying on ENTRESTO NDA 207620 at least until after the expiration of the 3-year exclusivity in February 2024. Upon expiration of the 3-year exclusivity period, an ANDA applicant would be required to submit a patent certification to the HFpEF Patents. ...an ANDA applicant cannot submit a section viii statement and labeling that proposes to omit the patented use in HFpEF patients. Petition response issued but the Agency is determining how to resolve any carve-out issues.

No Approval Actions (TA/AP) can be taken prior to contacting Policy Lead

No CRL can be issued prior to contacting Policy Lead;

(b)(4)

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Mayra
Pineiro Sanchez

Digitally signed by Mayra Pineiro Sanchez
Date: 9/22/2023 03:56:26PM
GUID: 508da702000288099b99e9faff8a6a27

ANDA Executive Summary

1. Application/Product Information

ANDA Number.	213748		
Review Cycle #	04		
Applicant Name	MSN Laboratories Private Limited		
Drug Product Name	Sacubitril and Valsartan		
Dosage Form. (click (+) for more than one)	Tablet		
Proposed Strength(s)	24 mg/26 mg, 49 mg /51 mg and 97 mg/103 mg		
Route of Administration (click (+) for more than one)	Oral		
Maximum Daily Dose	sacubitril 97 mg and valsartan 103 mg x 2/day		
Rx/OTC Dispensed	Rx		
Proposed Indication	Sacubitril and valsartan tablet is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (b)(4) and reduced ejection fraction.		
Drug Product Description	Refer to 3.2.P.1		
Co-packaged product information	N/A		
Device information, if any:	N/A		
Storage Temperature/ Conditions	Store at 25°C (77°F), excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from moisture.		
Review Team	Discipline	Primary	Secondary
	<i>Drug Substance</i>	Behnam Abdolalizadeh	Mayra Pineiro-Sanchez

	<i>Drug Product/ Labeling</i>	Behnam Abdolalizadeh	Mayra Pineiro-Sanchez
	<i>Manufacturing</i>	Amit Kokate	Jean Tang
	<i>Biopharmaceutics</i>	Ho-Pi Lin	N/A
	<i>Microbiology</i>	N/A	N/A
	<i>Other (specify):</i>	N/A	N/A
	<i>RBPM</i>	Candice Cottle-Delisle	
	<i>ATL</i>	Mayra Pineiro-Sanchez	
Consults	Discipline Consulted	Recommendation	Date

2. Submission Document(s) Reviewed

Submission(s) Assessed	Documents Date	Disciplines Affected
Original/Initial Submission	07/07/2019	All
Labeling-response to DRL	10/30/2019	Labeling
Quality/Response to Discipline Review Letter	2/27/2020	Quality
Resubmission/After Action- Complete Response	08/19/2020	Quality
Quality/Response To Information Request	08/28/2020	Quality
CR Response	02/09/2022	Quality
IR response	02/23/2022	Quality
CR Response	12/27/2022	Quality/Labeling
Quality/Response To Information Request	07/06/2023	Quality

3. Related/Supporting Documents

a. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Assessor/ Comments
(b)(4)	II	(b)(4)	Sacubitril and Valsartan	Adequate	07/12/2023	R05
	II		(b)(4)	Adequate	02/09/2022	
	II			Adequate	04/05/2022	
	IV					
	IV					
	IV					
	III					Refer to 3.2.P.7

b. Other Documents: IND, RLD, RS, Approved ANDA

Document	Application Number	Description
RLD	NDA 207620	ENTRESTO®

4. Final Overall recommendation – Approval

Deficiencies (if applicable):

NONE

Overall Quality Deficiencies - Optional (*Deficiencies that affect multiple sub-disciplines; for subheadings use the format shown, for all deficiencies.*)

1.

Drug Substance Deficiencies

1.

Drug Product Deficiencies

1.

Labeling Deficiencies *(Please contact OGD if you identify any Labeling deficiencies with your comments)*

1.

Manufacturing Deficiencies

1.

Biopharmaceutics Deficiencies

1.

Microbiology Deficiencies

1.

Other Deficiencies *(Specify discipline, such as Environmental. For consults such as Biostatistics, PharmTox, CDRH, Clinical, etc., include consult type and specify Quality discipline – example: Pharm/Tox consult for Drug Product)*

1.

Additional Comments:

In addition to responding to the deficiencies presented above, please note and acknowledge the following comment(s) in your response:

5. Basis for Recommendation

a. Summary of Rationale for Recommendation:

*The ANDA submitted on the basis of NDA 207620 (RLD), ENTRESTO® includes sufficient information to assure the identity, strength, purity, and quality of the drug product during the expiration dating period of 24 months. The applicant has provided acceptable raw material, in-process, and finished product controls and established an adequate dissolution specification (method and acceptance criteria) for routine quality control of the finished product. The overall facility assessment recommends approval and the labels** have adequate quality information. Therefore, from the quality perspective, this ANDA is recommended for approval.*

(b)(4)

(b)(4)

b. Recommendation by Subdiscipline:

Drug Substance: ADEQUATE

Provide justification(s) (for major deficiencies only):

(Click link to view [Justification Statements](#))

1.

Drug Product: ADEQUATE

Provide justification(s) (for major deficiencies only):

(Click link to view [Justification Statements](#))

1.

Quality Labeling: ADEQUATE

Provide justification(s) (for major deficiencies only):

(Click link to view [Justification Statements](#))

1.

Manufacturing: ADEQUATE

Provide justification(s) (for major deficiencies only):

(Click link to view [Justification Statements](#))

1.

Biopharmaceutics: ADEQUATE

Provide justification(s) (for major deficiencies only):

(Click link to view [Justification Statements](#))

1.

Microbiology: N/A

Provide justification(s) (for major deficiencies only):

(Click link to view [Justification Statements](#))

1.

Environmental: N/A

Provide justification(s) (for major deficiencies only):

(Click link to view [Justification Statements](#))

1.

6. Life-Cycle Considerations

Established Conditions per ICH Q12: No

Comments:

Comparability Protocols (PACMP): No

Comments:

Additional Comments:

OGD Policy Alert: **YES** (05SEP2023)

FDA-2021-P-1286 (NDA 207620)

Entresto sacubitril; valsartan tablets

Petition requests that the FDA refrain from approving an ANDA relying on ENTRESTO NDA 207620 at least until after the expiration of the 3-year exclusivity in February 2024. Upon expiration of the 3-year exclusivity period, an ANDA applicant would be required to submit a patent certification to the HFpEF Patents. ...an ANDA applicant cannot submit a section viii statement and labeling that proposes to omit the patented use in HFpEF patients. Petition response issued but the Agency is determining how to resolve any carve-out issues.

No Approval Actions (TA/AP) can be taken prior to contacting Policy Lead

No CRL can be issued prior to contacting Policy Lead;

(b)(4)

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Mayra
Pineiro Sanchez

Digitally signed by Mayra Pineiro Sanchez
Date: 9/22/2023 03:56:26PM
GUID: 508da702000288099b99e9faff8a6a27

RECOMMENDATION

☐ Complete Response-Major
☐ Complete Response-Minor
☐ Discipline Review Letter (DRL)
☐ Information Request—IR x Days
☒ Approval

ANDA 213748 Assessment Cycle #04

Drug Product Name	Sacubitril and Valsartan Tablets
USP Monograph	☐ Yes ☒ No
Strength	24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg
Dosage Form	Tablets
Route of Administration	Oral
Rx/OTC Dispensed	☒ Rx ☐ OTC
ANDA Applicant	MSN Laboratories Private Limited
Drug Product Manufacturer	☒ Same as the Applicant ☐ Different from the Applicant (see below)
US agent, if applicable	☐ N/A ☒ (See Below) MSN Pharmaceuticals Inc. 20 Duke Road, Piscataway, NJ 08854-3714
Proposed Indication	Sacubitril and Valsartan Tablets indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (b)(4) and reduced ejection fraction.

Submission(s) Assessed	Document Date	Discipline(s) Affected
IR Response	7/6/2023	Quality
CR 03	12/27/2022	Quality
CR 02	2/9/2022	Quality
CR 01	8/19/2020	Quality
Amendment-Response to DRL	2/27/2020	Quality
Original	7/8/2019	All
Labeling-Response to Discipline Review Letter*	10/30/2019	Labeling

*Preparation of oral suspension added in label to be in line with RLD, but no supporting quality information provided

Original & DRL assessed by 1ry: Qiuxia Wang; QAL: Raghu Samy
 Submission CR 01 and CR 02 assessed by B. Abdolizadeh
 Submission CR 03 assessed by B. Abdolizadeh in review R04
 Submission IR response assessed by B. Abdolizadeh in review R04

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QUALITY ASSESMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Reviewed	Comments
(b)(4)	II	(b)(4)	Sacubitril and Valsartan	Adequate, R05	07/12/2023	D. Yu
	II			Adequate, R04	02/09/2022	D. Yu
	II		(b)(4)	Adequate, R05	04/05/2022	D. Johnson
	Other DMF: ☐ N/A ☒ (See Below)					
	III	(b)(4)				
	III					
	III					
	III					
	III					
	III					
III						
III						
IV						
IV						
Other						

(b)(4)

B. OTHER DOCUMENTS: IND, RLD, RS, Approved ANDA

Document	Application Number	Brand Name	Description
NDA	207620	ENTRESTO®	Sacubitril and Valsartan Tab, 24/26, 49 /51, 97 /103 mg

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH-ODE	N/A			
CDRH-OC	N/A			
Clinical	N/A			
Other	N/A			

Review of Firm's Response to Deficiencies

Review of Amendment Dated 7/6/2023

This amendment is in response to complete response letter was issued on June 29, 2023.

The following link is for the responses to CR deficiencies:

[ANDA213748 \(213748 - 0014 - \(15\) - 2023-07-06 - ORIG-1 /Multiple Categories/Subcategories\) - response-to-ir-0014](#)

Comment 1:

(b)(4)

Applicant Response:

(b)(4)

Reviewer's Comment

adequate

(b)(4)

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**OLDP Assessment Team: 1ry: Qiuxia Wang; QAL:
Raghu Samy**

CHAPTER I: DRUG SUBSTANCE

[IQA ANDA Assessment Guide Reference](#)

Drug Substance Name	Sacubitril and Valsartan
DMF Number (If Applicable)	
DMF Status	Adequate
DMF Holder	(b)(4)

Overall Assessment Recommendation for DS:

Adequate

Theme:

☒ N/A	☐ Other (Requires Division Director Approval)
☐ DMF	☐ Due to Consult
☐ New DS Batch	

Justification: view justification statements found at: [Justification Statements](#)

Paste appropriate justification statement(s) here or insert "N/A" if not applicable.
Other (Requires Division Director Approval)- Assessor writes justification here if "other" selected as theme.

Justification for Major from DMF review

Highlight Key Issues from Last Cycle and Their Resolution:

No Key issues with DS from last cycle review

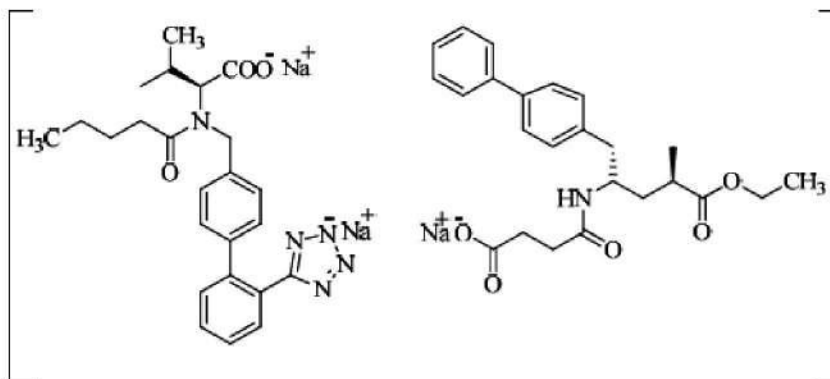
Concise Description of Outstanding Issues:

N/A - No Deficiencies with DS in the ANDA

Select Number of Approved Comparability Protocols: 00

S.1 GENERAL INFORMATION

Recommended International Nonproprietary Name	Sacubitril and Valsartan
USAN	Sacubitril and Valsartan
Chemical Name(s)	Tri sodium (4- { [(1 S,3R)-1-([1,1'-biphenyl] 4-ylmethyl)-4-ethoxy-3-methyl-4-oxobutyl]amino } -4-oxobutanoate)-(N-pentanoyl-N-{ [2'-(1H-tetrazol-1-id-5-yl)[1,1'-biphenyl]-4-yl]methyl }-L-valinate)
CAS Number	936623-90-4
Therapeutic Category	To treat heart failure
Structure	



Molecular Formula	C ₄₈ H ₅₅ N ₆ O ₈ Na ₃
Molecular Weight	912.96

Description White to almost white powder.

(b)(4)

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(b)(4)

Assessment:

Adequate

Deficiency in Review 1:

(b)(4)

(b)(4) (Satisfactorily
addressed in the amendment dated 2/27/2020)

Post-Approval Stability Protocol and Commitment

Assessment:

Adequate

Refer to DMF review

R REGIONAL INFORMATION

Comparability Protocols ☒ N/A ☐ (See Below)

Assessment:

Choose an item.

Lifecycle Management Considerations

DRUG SUBSTANCE LIST OF DEFICIENCIES:

N/A

CHAPTER II: DRUG PRODUCT

[IQA ANDA Assessment Guide Reference](#)

Overall Assessment Recommendation:

Adequate

Theme:

☒ N/A	☐ Unacceptable Analytical Methods
☐ Unqualified Impurity	☐ Application Quality
☐ New DP Batch	☐ Pharmaceutical Equivalence
☐ Product Design	☐ Product Safety
☐ Failing Stability Data	☐ Other (Requires Division Director Approval)
☐ Application Completeness	☐ Due to Consult

Justification: view justification statements found at: [Justification Statements](#)

Paste appropriate justification statement(s) here or insert "N/A" if not applicable.
Other (Requires Division Director Approval)- Assessor writes justification here if "other" selected as theme.

Assessment Summary:

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking After Assessment Cycle #	Comments

Note: This table will be updated in Executive Summary at time of approval.

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Concise Description of Outstanding Issues (List Bullet Points with Key Information and Update as Needed): N/A

Select Number of Approved Comparability Protocols: 0

List Current Quality Endorsement Status:

- USP monograph for Drug Product and compliance (current USP) – status: not USP
- Dissolution status: dissolution method and specifications are finalized with Biopharmaceutics.
- Elemental impurity compliance with ICH Q3D – status: adequate

- Number of Comparability protocols included: 0

P.1 DESCRIPTION AND COMPOSITION

The quantitative composition and function of each excipient in the drug product is listed.

Ingredients	Functions	24 mg/ 26 mg (mg/tablet)	% w/w	49 mg/ 51 mg (mg/tablet)	% w/w	97 mg/ 103 mg (mg/tablet)	% w/w	Maximum Levels (dosage per unit) (mg)	IIG Limit for Oral Route of Administration (mg)
(b)(4)									
Sacubitril and Valsartan**	Active ingredient	(b)(4)							
Microcrystalline Cellulose**	(b)(4)								
(b)(4) } USP-NF									
Crospovidone									
(b)(4) } USP-NF									
Croscarmellose Sodium									
(b)(4) } USP-NF									
Colloidal Silicon Dioxide									
(b)(4) } USP-NF	(b)(4)								
Talc (b)(4) } USP									
Magnesium Stearate (b)(4) } USP-NF									
(b)(4)	(b)(4)								
(b)(4)	(b)(4)								
Black Iron Oxide	(b)(4)								
(b)(4)									
Iron Oxide Yellow									
Iron Oxide Red									
(b)(4)									

Ingredients	Functions	24 mg/ 26 mg (mg/tablet)	% w/w	49 mg/ 51 mg (mg/tablet)	% w/w	97 mg/ 103 mg (mg/tablet)	% w/w	Maximum Levels (dosage per unit) (mg)	IIG Limit for Oral Route of Administration (mg)
(b)(4)									
Coated Tablet weight		103.000	100.00	206.000	100.00	412.000	100.00	-	-

(b)(4)

RLD	Test Product
Microcrystalline Cellulose	Microcrystalline Cellulose (b)(4)
Crospovidone	Crospovidone (b)(4)
Low-substituted hydroxypropyl Cellulose	Croscarmellose sodium
Colloidal silicon dioxide	Colloidal silicon dioxide
Talc	Talc (b)(4)
Magnesium stearate	Magnesium stearate
(b)(4)	
Hypromellose	Hypromellose
Titanium dioxide	Titanium dioxide
Macrogol 4000	Macrogol/ (b)(4)
(b)(4)	(b)(4)
Iron oxide red	Red iron oxide (b)(4)
Iron oxide Black	Black Iron oxide (b)(4)
(b)(4)	
(b)(4)	(b)(4)
Iron oxide yellow	
(b)(4)	
(b)(4)	
(b)(4)	
(b)(4)	(b)(4)

RLD	Test Product
(b)(4)	

Assessment:

Adequate

Strength	Product Description
24 mg/ 26 mg	Purple colored, oval shaped, biconvex, film coated tablets one side debossed with 'M' and other side debossed with 'S1' (b)(4)
49 mg/51 mg	Light yellow to yellow colored, oval shaped, biconvex, film coated tablets one side debossed with 'M' and other side debossed with 'S2' (b)(4)
97 mg/ 103 mg	Light pink to pink colored, oval shaped, biconvex, film coated tablets one side debossed with 'M' and other side debossed with 'S3' (b)(4)

The firm provided adequate information regarding to components and composition of the drug product.

(b)(4)

There are some minor differences in compositions between the generic proposed formulation and the formulation of the reference product, but they should not have any effects on the quality of the drug products.

However, whether the difference between this proposed formulation and the RLD present any potential concerns with respect to therapeutic equivalence of drug product would rely on the evaluation of Division of Bioequivalence.

The size and shape of generic Sacubitril and Valsartan tablets meets the requirements as per "Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules" as shown in the table below.

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Methods Validation or Verification Package

Assessment:

Adequate

Comparability Protocols

Assessment:

N/A

Choose an item.

Lifecycle Management Considerations

DRUG PRODUCT LIST OF DEFICIENCIES)

N/A

CHAPTER III: ENVIRONMENTAL

R REGIONAL INFORMATION

Environmental

Assessment:

Adequate

CHAPTER IV: LABELING

R REGIONAL INFORMATION

1.14 Labeling

Labeling & Prescribing Information

DESCRIPTION (Rx insert or Active Ingredient(s), and Inactive Ingredients in DRUG FACTS for OTC):

Is the information accurate? ☒ Yes ☐ No

If "No," explain.

Is the drug product subject of a USP monograph? ☐ Yes ☒ No

If "Yes," does labeling have accurate USP statement in the DESCRIPTION (for Rx) or Other Information section of DRUG FACTS (for OTC)?

☐ Yes ☐ No ☐ Statement not needed

If NO, what is/are the needed statement(s)? _____

HOW SUPPLIED section (Rx insert) or Storage (in DRUG FACTS for OTC)

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Is tamper evident feature provided in the container/closure for the OTC products or Controlled Substance (CII – CIV) products? ☐ Yes ☐ No
☒ N/A (NOT OTC or Controlled Substance)

If "No," explain.

For solid oral drug products, only: drug product length(s) of commercial batch(es):

ANDA Strength	Length (MM)	Imprint Code
24 mg/ 26 mg	10.00 x 4.00	one side debossed with 'M' and other side debossed with 'S1'
49 mg/ 51 mg	13.00 x 5.10	one side debossed with 'M' and other side debossed with 'S2'
97 mg/ 103 mg	15.00 x 5.90	one side debossed with 'M' and other side debossed with 'S3'

Send issue to the Labeling assessor through the Platform with a list of quality-related labeling deficiencies and also record reference number or link for all the issues:

Issue Description	Issue Reference Number or Link

LABELING LIST OF DEFICIENCIES

N/A

ATTACHMENT II: List of All Deficiencies

N/A



Behnam
Abdolzadeh

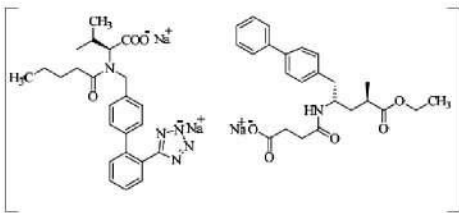
Digitally signed by Behnam Abdolzadeh
Date: 8/09/2023 05:52:57AM
GUID: 51dc72810000c6e47569a654b09e35e0



Mayra
Pineiro Sanchez

Digitally signed by Mayra Pineiro Sanchez
Date: 8/08/2023 09:43:48PM
GUID: 508da702000288099b99e9faff8a6a27

MANUFACTURING INTEGRATED ASSESSMENT

Application ID	ANDA 213748
Drug Product Name	Sacubitril and Valsartan Tablets  CAS #: 936623-90-4 Molecular Formula: C ₄₈ H ₅₅ N ₆ O ₈ Na ₃ Molecular Weight: 912.96 g/mol Prioritization Factor: First Generic - Granted
Strengths	24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg
Dosage Form	Tablet
Administration Route	Oral
Indication	Sacubitril and valsartan tablet is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (b)(4) and reduced ejection fraction.
Applicant Name	MSN Laboratories Private Limited
RLD Number	N207620 ENTRESTO

Reviewer's Note:

Blue font refers to the current Amendment-12 (SD#12 received 02/09/2022)/review cycle

Black font refers to the previous review cycle (SD#9 received 08/28/2021)

I. Manufacturing Summary

Facility Assessment Recommendation: Adequate

Process Assessment Recommendation: Adequate

(b)(4)

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VI. Signature Block

Round#	Primary Name	Secondary & Other Names	Date of Completion	Assessment Outcome	Facility OMIR
1	Jingbo Xiao 09/03/2019 11/22/2019 12/16/2019	Vaikunth S. Prabhu 09/05/2019 12/12/2019 12/17/2019	12/17/2019	IR	TBD
2	Jingbo Xiao 03/04/2020 04/07/2020 05/27/2020	Vaikunth S. Prabhu 03/19/2020 04/07/2020 05/27/2020	5/27/2020	CR Major	Withheld
3	Amit Kokate 1/25/2021	Jean Tang 2/1/2021	3/15/2021	CR Minor	Approve
4	Amit Kokate	Jean Tang	3/29/2022	Adequate	Approve



Amit
Kokate

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Jean
Tang

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Date: 4/11/2022 12:06:23PM
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BIOPHARMACEUTICS ANDA REVIEW	
Application No.	ANDA 213748-ORIG-1
Applicant	MSN Laboratories Private Ltd.
Product Name/Strength	Sacubitril/Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg
Dosage Form/ Route of Administration:	Tablets/Oral
Indication	Indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure
Submission Date(s)	07/07/2019 – Original Submission 02/ 27/2020 – IR Response
RLD/RS	ENTRESTO® Tablets, 24mg/26mg,49mg/51mg & 97mg/103mg (NDA# 207620)
Primary Reviewer	Mathew John, Ph.D.
Secondary Reviewer	Om Anand, Ph.D.
Recommendation	Inadequate-Minor

Executive Summary: This Biopharmaceutics Review evaluates data supporting the adequacy of the proposed dissolution method and acceptance criteria for the proposed drug product.

The proposed drug product, Sacubitril/Valsartan Tablets,

(b)(4)

(b)(4)

The Applicant originally proposed to use

(b)(4)

(b)(4) In the Original submission, the Applicant did not provide adequate data demonstrating the suitability of the originally proposed dissolution method (b)(4)

(b)(4)

In a response (dated 02/27/2020,) to IRs, the Applicant revised the dissolution method,

(b)(4)

¹ FDA Recommended Dissolution Methods

² \\cdsesub1\evsprod\anda213748\0005\m2\27-clin-sum\pivotal-cdp-report.pdf

drug product. The updated dissolution method and acceptance criterion submitted by the Applicant are tabulated in Table 1 below.

Table 1: Updated dissolution method and acceptance criterion proposed by the Applicant

Method Source	USP Apparatus	Speed (RPMs)	Medium	Volume/Temp (mL/°C)	Proposed Acceptance Criterion
(b)(4)					

The newly proposed dissolution method is acceptable. However, the proposed acceptance criterion is (b)(4) and not acceptable, therefore an IR will be sent to revise the dissolution acceptance criteria to NLT (b)(4) % (Q) in 20 minutes” [for both sacubitril and valsartan] for all strengths of the drug product.

Biopharmaceutics Recommendation: The Biopharmaceutics recommendation for ANDA 213748 for the proposed Sacubitril/Valsartan Tablets, is **pending** due to the outstanding response to the Information Request (IR) comment regarding the dissolution acceptance criterion.

Reviewer's Assessment

1. **Solubility:** (b)(4)

(b)(4)

2. **Formulation** (b)(4)

(b)(4)

3. **Bioequivalence and PK Characteristics of the drugs:** T_{max} for sacubitril, LBQ657 (active metabolite of sacubitril), and valsartan are 0.5 hours, 2 hours, and 1.5 hours, respectively. The oral absolute bioavailability of sacubitril is estimated to be $\geq 60\%$. [Ref. Labeling]. The Applicant performed in-vivo bioequivalence studies using the proposed test and the RS products. The Applicant submitted bioequivalence study results were evaluated by the Division of Bioequivalence / OGD and was deemed inadequate⁵.

4. **Dissolution Method:** In the original submission, the Applicant used the dissolution method

(b)(4)

In the response to the IRs⁶, the Applicant accepted FDA's recommendation and adopted⁷ ☐

(b)(4)

³ \\cdsesub1\evsprod\ANDA213748\0000\m3\32-body-data\32s-drug-sub\sacu-vals-msn-life-sciences-pvt-ltd\32s1-gen-info

⁴ \\cdsesub1\evsprod\anda213748\0000\m2\23-qos\qos-ds-word.doc

⁵ <https://panorama.fda.gov/document/preview?versionID=5df7d772007be5324bcd0016b3019064&ID=5de99fbb002c8bc85574b04e53bbcd21>

⁶ \\cdsesub1\evsprod\anda213748\0005\m1\us\1-2-cover-letters\response-to-drl-0005.pdf

⁷ \\cdsesub1\evsprod\anda213748\0005\m2\27-clin-sum\pivotal-cdp-report.pdf

(b)(4) Therefore, based on the totality of the data and justifications provided by the Applicant, the newly proposed dissolution method (Basket/75 rpm) is acceptable.

5. **Dissolution Acceptance Criterion:** Using the new dissolution method, the dissolution data of all batches of both sacubitril and valsartan in 24 mg/26 mg and 49 mg/51 mg Tablet strengths show a (b)(4). The dissolution data for all batches of 97/103 mg Tablet strength exhibit a (b)(4) % in 20 minutes⁸. The Applicant proposed acceptance criterion is (b)(4) and therefore an IR will be sent to tighten the dissolution acceptance criteria as NLT (b)(4) % (Q) in 20 minutes” [for both sacubitril and valsartan] for all strengths of the drug product.

6. **Dissolution Risk/Mitigation Assessment:** Biopharmaceutics/dissolution risk is relatively high because (b)(4). The dissolution method and acceptance criterion are set appropriately to mitigate the risk of the change in the drug product performance.

Additional Note: The originally posted dissolution method (b)(4)

(b)(4)
(b)(4) the Applicant proposed dissolution method using USP Type-I basket method at rotational speed of 75 rpm. This new method was found to be acceptable for the NDA and therefore, i) due to the limitations of the original method; and ii) due to the change in the dissolution method followed by the NDA; the FDA dissolution database was updated with the new dissolution method [900 mL of Phosphate Buffer, pH 6.8 using USP apparatus 1 (basket) at 75 rpm].

⁸ <\\cdsesub1\evsprod\anda213748\0005\m2\27-clin-sum\pivotal-cdp-report.pdf>

LIST OF COMMENTS FOR THE INFORMATION REQUEST # 2

Based on the provided information and data, the proposed dissolution method [USP 1 (basket) at 75 rpm/900 mL of pH 6.8 phosphate buffer] is deemed adequate for quality control testing of the proposed drug product. However, the provided dissolution data support a dissolution acceptance criterion and therefore the proposed acceptance criterion is not acceptable. Implement the following dissolution acceptance criterion for all strengths of your proposed product, Sacubitril and Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg and 97/103 mg:

“NLT % (Q) in 20 minutes” [for both sacubitril and valsartan]

Update your drug product release and stability specifications accordingly. In addition, please be advised, that all proposed exhibit batches are expected to meet these revised dissolution specifications in your stability program through your proposed expiry period. If dissolution failures are observed on stability, these should be described. Discuss any corrective actions to avert such dissolution failures and provide data from a new batch to demonstrate correction of the issue, if needed.

APPENDIX I

Information Request [dated 12/23/2019] and Response [dated 02/27/2020]

1. The proposed dissolution method (b)(4)
(b)(4) is not acceptable at this stage because (b)(4)
(b)(4)
(b)(4)

The limited data/information provided are not adequate to demonstrate the suitability/discriminating ability of the proposed dissolution method for your proposed drug product. Please note that the discriminating ability of the dissolution method should be investigated towards the critical material attributes (CMAs), critical process parameters (CPPs) and critical formulation variables (CFVs). In your response, justify the selection of the selected attributes /variables and their levels for demonstrating the discriminating ability of the proposed dissolution method. Described below are our recommendations with respect to proper investigation for the discriminating ability of the proposed dissolution method:

- i. Provide a list of CMAs, CPPs and CFVs affecting the dissolution and establish that your method is discriminating towards those CMAs (including the drug substance particle size distribution), CPPs and CFVs which affect dissolution. In general, the testing conducted to demonstrate the discriminating ability of the dissolution method should compare the dissolution profiles of the proposed drug product(target) and the formulations/product that are intentionally manufactured with meaningful variations, i.e., aberrant formulations and manufacturing conditions with $\pm 10\text{-}20\%$ change to the specification-ranges of these variables for the most relevant CMA's and CPPs.
- ii. In addition, if available, data can be submitted showing that the selected dissolution method is able to reject batches that are not bioequivalent. Supportive dissolution data may also be submitted showing that the selected dissolution method can detect the change(s) in the drug product occurring during the accelerated and stressed conditions.
- iii. Provide i) the manufacturing date, storage conditions and the age of the batches used in the above studies, ii) the number of dosage units used to generate the dissolution data, iii) complete dissolution data (individual, mean, cv%) in tabulated format, and iv) graphic presentation for the mean dissolution data for each table.

The adequacy of the proposed dissolution acceptance criterion will be determined after the accessing the above requested information.

The limited in dissolution data demonstrate that the dissolution of some units of the test product remains incomplete using your proposed method, for example some units of Batch # DT1812065 dissolved (b)(4) % and a mean of (b)(4) % at - minutes. Explain the root cause of the incomplete dissolution of the proposed drug product using your proposed method. Support your explanation with appropriate data. Submit dissolution

(b)(4)

2. Note that the FDA dissolution database[https://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_SearchResults.cfm] has been updated with a new dissolution method [900 mL of Phosphate Buffer, pH 6.8 using USP apparatus 1 (basket) at 75 rpm]. Please submit dissolution data [(N=12, individual, mean, cv%)] for all your exhibits batches using this method. If using the originally proposed dissolution method (b)(4) the dissolution of your proposed drug product remains incomplete or (b)(4), then you may consider this new FDA method for the quality control testing of your proposed drug product. If you choose to do so, the please submit the information/data showing the suitability/discriminating ability of the proposed dissolution method for your proposed drug product, as per above recommendations regarding the demonstration of the suitability/discriminating ability.

Applicant's Response [dated 02/27/2020]:**The Applicant's detailed response is available at the following link⁹:**

The Applicant adopted the dissolution method currently available in the FDA dissolution data base for this drug product as tabulated in Table 1. The Applicant has also submitted the comparative dissolution profiles in section 2.7 of the submission as per the current dissolution method. The Applicant has also studied the discriminative ability of the method in terms of different

(b)(4) The Applicant also explained that they observed a complete release of the drug from the drug product using the newly proposed dissolution method.

Reviewer's Assessment of the response: The Applicant proposed new dissolution method for the proposed drug product is acceptable. However, the proposed dissolution acceptance criterion of Q (b)(4) for all strengths of both Sacubitril and Valsartan is (b)(4) and therefore, the Applicant will be recommended to implement a (b)(4) dissolution acceptance criterion (Please see IR # 2).

⁹ \\cdsesub1\evsprod\anda213748\0005\m1\us\1-2-cover-letters\response-to-drl-0005.pdf

APPENDIX II

Dissolution Profile Data

Figure 1: In vitro dissolution profile of drug product strength 97 mg / 103 mg biobatch # DT1812070 using (b)(4)

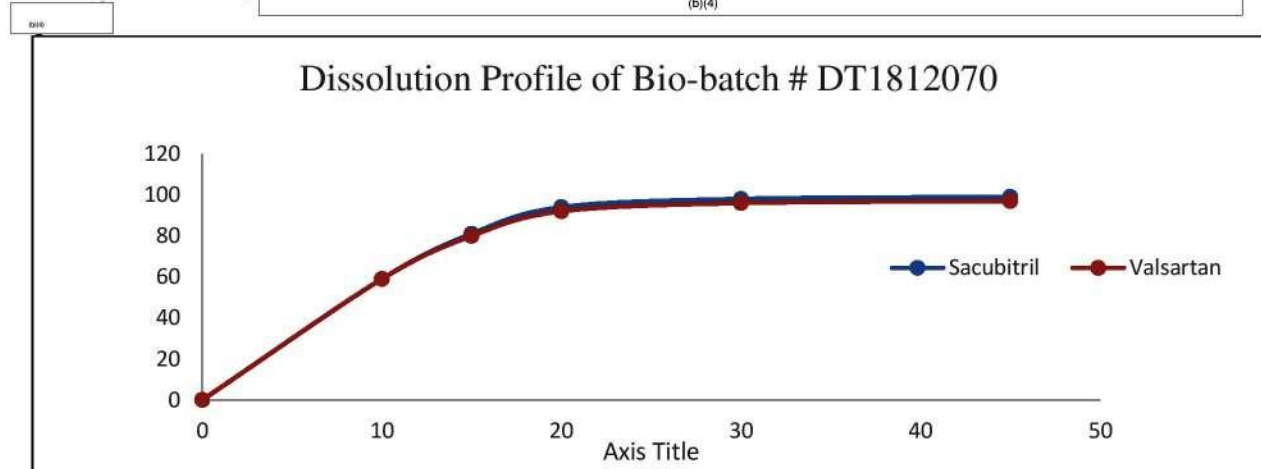
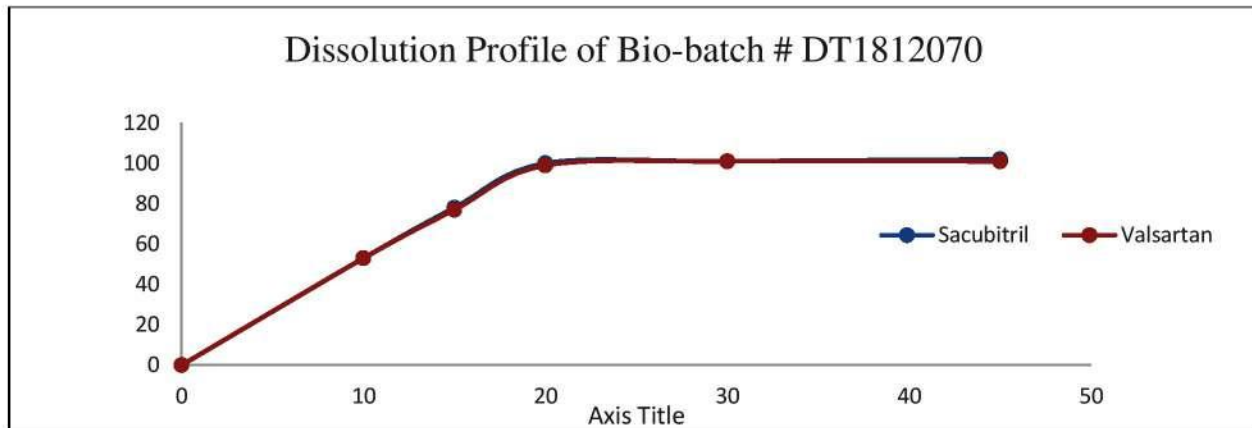


Figure 2: In vitro dissolution profile of drug product strength 97 mg / 103 mg biobatch # DT1812070 using the current method in the FDA dissolution database (USP Apparatus 1/ 75 rpm)¹¹



¹⁰ <\\cdsesub1\evsprod\anda213748\0000\m2\27-clin-sum\pivotal-biosummary-tables-pdf.pdf>

¹¹ <\\cdsesub1\evsprod\anda213748\0005\m2\27-clin-sum\pivotal-cdp-report.pdf>

Using the newly proposed dissolution method, the biobatch and all the exhibit batches shows % drug release by 20 minutes. The submitted dissolution data supports a dissolution acceptance criterion (refer IR #2) and will be communicated to the Applicant.



Om
Anand

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Mathew
John

Digitally signed by Mathew John
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BIOPHARMACEUTICS ASSESSMENT	
Application No.	ANDA-213748-ORIG-1-AMEND-8
Submission Type	Solicited Major Amendment
Applicant	MSN LABORATORIES PRIVATE LIMITED
Product Name	Sacubitril and Valsartan Tablets
Dosage Form/Strengths	IR Tablet; 24 mg/26 mg, 49 mg/51 mg and 97mg/103 mg
Route of Administration	Oral
Indication	(b)(4)
Submission Date	8/19/20
Goal Date	4/18/2021
Primary Reviewer	Ho-Pi Lin, Ph.D.
Secondary Reviewer	N/A
Recommendation	ADEQUATE

EXECUTIVE SUMMARY

Background:

This amendment (#8) was submitted in response to the complete response (CR) letter issued on 6/8/2020 for the original submission. Previous assessment was documented in Panorama.¹ The assessment concluded inadequate was due to inadequate dissolution acceptance criterion.

Previous CR Comments

Based on the provided information and data, the proposed dissolution method [USP 1 (basket) at 75 rpm/900 mL of pH 6.8 phosphate buffer] is deemed adequate for quality control testing of the proposed drug product. However, the provided dissolution data support a dissolution acceptance criterion and therefore the proposed acceptance criterion is not acceptable. Implement the following dissolution acceptance criterion for all strengths of your proposed product, Sacubitril and Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg and 97/103 mg:
“NLT % (Q) in 20 minutes” [for both sacubitril and valsartan]

¹

<https://panorama.fda.gov/internal/document/preview?versionID=5eac76cf01b56ba5c2cd6ace37d442ec&ID=5dfd0f2d0014e7e092033c3228682dac>

Update your drug product release and stability specifications accordingly. In addition, please be advised, that all proposed exhibit batches are expected to meet these revised dissolution specifications in your stability program through your proposed expiry period. If dissolution failures are observed on stability, these should be described. Discuss any corrective actions to avert such dissolution failures and provide data from a new batch to demonstrate correction of the issue, if needed.

Biopharmaceutics Assessment:

The Applicant accepted² and implemented³ the recommended criterion. The response is acceptable.

Recommendation:

This ANDA 213748 is recommended for approval from a biopharmaceutics perspective.

Approved disintegration method and acceptance criterion/criteria:

USP Apparatus	Speed	Medium/Temperature	Acceptance criterion(a)
I (Basket)	75 rpm	pH 6.8 phosphate buffer/37°C 900 ml	Q=□% in 20 minutes (Sacubitril & Valsartan)

² Page 5 in <file:///C:/cdsesub1/evsprod/ANDA213748/0007/m1/us/1-2-cover-letters/response-to-crl-0007.pdf>

³ <file:///C:/cdsesub1/evsprod/ANDA213748/0007/m3/32-body-data/32p-drug-prod/sac-vlsrtn-tab-msn-lab/32p5-contr-drug-prod/32p51-spec/specifications.pdf>



Ho-Pi
Lin



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Mayra
Pineiro Sanchez

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RECOMMENDATION

☐ Complete Response-Major
☐ Complete Response-Minor
☐ Discipline Review Letter (DRL)
☐ Information Request—IR x Days
☒ Approval

ANDA 213748 Assessment Cycle #04

Drug Product Name	Sacubitril and Valsartan Tablets
USP Monograph	☐ Yes ☒ No
Strength	24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg
Dosage Form	Tablets
Route of Administration	Oral
Rx/OTC Dispensed	☒ Rx ☐ OTC
ANDA Applicant	MSN Laboratories Private Limited
Drug Product Manufacturer	☒ Same as the Applicant ☐ Different from the Applicant (see below)
US agent, if applicable	☐ N/A ☒ (See Below) MSN Pharmaceuticals Inc. 20 Duke Road, Piscataway, NJ 08854-3714
Proposed Indication	Sacubitril and Valsartan Tablets indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (b)(4) and reduced ejection fraction.

Submission(s) Assessed	Document Date	Discipline(s) Affected
IR Response	7/6/2023	Quality
CR 03	12/27/2022	Quality
CR 02	2/9/2022	Quality
CR 01	8/19/2020	Quality
Amendment-Response to DRL	2/27/2020	Quality
Original	7/8/2019	All
Labeling-Response to Discipline Review Letter*	10/30/2019	Labeling

*Preparation of oral suspension added in label to be in line with RLD, but no supporting quality information provided

Original & DRL assessed by 1ry: Qiuxia Wang; QAL: Raghu Samy
 Submission CR 01 and CR 02 assessed by B. Abdolizadeh
 Submission CR 03 assessed by B. Abdolizadeh in review R04
 Submission IR response assessed by B. Abdolizadeh in review R04

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QUALITY ASSESMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Reviewed	Comments
(b)(4)	II	(b)(4)	Sacubitril and Valsartan	Adequate, R05	07/12/2023	D. Yu
	II			Adequate, R04	02/09/2022	D. Yu
	II			Adequate, R05	04/05/2022	D. Johnson
	Other DMF: ☐ N/A ☒ (See Below)					
	III	(b)(4)				
	III					
	III					
	III					
	III					
	III					
III						
III						
IV						
IV						
IV						
Other						

(b)(4)

B. OTHER DOCUMENTS: IND, RLD, RS, Approved ANDA

Document	Application Number	Brand Name	Description
NDA	207620	ENTRESTO®	Sacubitril and Valsartan Tab, 24/26, 49 /51, 97 /103 mg

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH-ODE	N/A			
CDRH-OC	N/A			
Clinical	N/A			
Other	N/A			

Review of Firm's Response to Deficiencies

Review of Amendment Dated 7/6/2023

This amendment is in response to complete response letter was issued on June 29, 2023.

The following link is for the responses to CR deficiencies:

[ANDA213748 \(213748 - 0014 - \(15\) - 2023-07-06 - ORIG-1 /Multiple Categories/Subcategories\) - response-to-ir-0014](#)

Comment 1:

(b)(4)

Applicant Response:

(b)(4)

Reviewer's Comment

adequate

(b)(4)

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**OLDP Assessment Team: 1ry: Qiuxia Wang; QAL:
Raghu Samy**

CHAPTER I: DRUG SUBSTANCE

[IQA ANDA Assessment Guide Reference](#)

Drug Substance Name	Sacubitril and Valsartan
DMF Number (If Applicable)	(b)(4)
DMF Status	Adequate
DMF Holder	(b)(4)

Overall Assessment Recommendation for DS:

Adequate

Theme:

☒ N/A	☐ Other (Requires Division Director Approval)
☐ DMF	☐ Due to Consult
☐ New DS Batch	

Justification: view justification statements found at: [Justification Statements](#)

Paste appropriate justification statement(s) here or insert "N/A" if not applicable.
Other (Requires Division Director Approval)- Assessor writes justification here if "other" selected as theme.

Justification for Major from DMF review

Highlight Key Issues from Last Cycle and Their Resolution:

No Key issues with DS from last cycle review

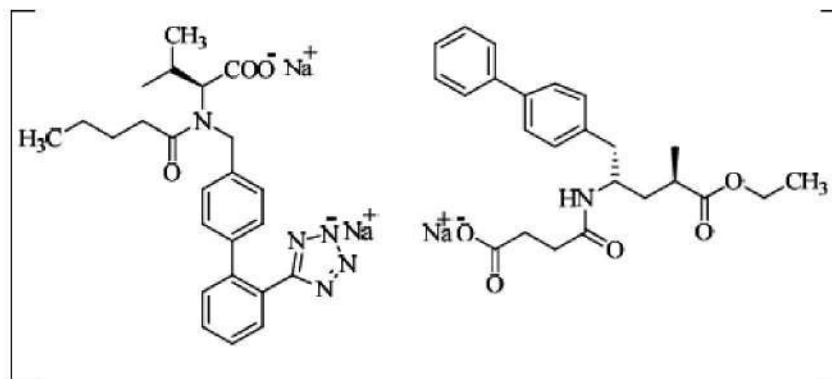
Concise Description of Outstanding Issues:

N/A - No Deficiencies with DS in the ANDA

Select Number of Approved Comparability Protocols: 00

S.1 GENERAL INFORMATION

Recommended International Nonproprietary Name	Sacubitril and Valsartan
USAN	Sacubitril and Valsartan
Chemical Name(s)	Tri sodium (4- { [(1 S,3R)-1-([1,1'-biphenyl] 4-ylmethyl)-4-ethoxy-3-methyl-4-oxobutyl]amino } -4-oxobutanoate)-(N-pentanoyl-N-{[2'-(1H-tetrazol-1-yl-5-yl)[1,1'-biphenyl]-4-yl]methyl }-L-valinate)
CAS Number	936623-90-4
Therapeutic Category	To treat heart failure
Structure	



Molecular Formula C₄₈H₅₅N₆O₈Na₃

Molecular Weight 912.96

Description White to almost white powder.

(b)(4)

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DRUG SUBSTANCE LIST OF DEFICIENCIES:

N/A

CHAPTER II: DRUG PRODUCT

[IQA ANDA Assessment Guide Reference](#)

Overall Assessment Recommendation:

Adequate

Theme:

☒ N/A	☐ Unacceptable Analytical Methods
☐ Unqualified Impurity	☐ Application Quality
☐ New DP Batch	☐ Pharmaceutical Equivalence
☐ Product Design	☐ Product Safety
☐ Failing Stability Data	☐ Other (Requires Division Director Approval)
☐ Application Completeness	☐ Due to Consult

Justification: view justification statements found at: [Justification Statements](#)

Paste appropriate justification statement(s) here or insert "N/A" if not applicable.
Other (Requires Division Director Approval)- Assessor writes justification here if "other" selected as theme.

Assessment Summary:

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking After Assessment Cycle #	Comments

Note: This table will be updated in Executive Summary at time of approval.

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Concise Description of Outstanding Issues (List Bullet Points with Key Information and Update as Needed): N/A

Select Number of Approved Comparability Protocols: 0

List Current Quality Endorsement Status:

- USP monograph for Drug Product and compliance (current USP) – status: not USP
- Dissolution status: dissolution method and specifications are finalized with Biopharmaceutics.
- Elemental impurity compliance with ICH Q3D – status: adequate

- Number of Comparability protocols included: 0

P.1 DESCRIPTION AND COMPOSITION

The quantitative composition and function of each excipient in the drug product is listed.

Ingredients	Functions	24 mg/ 26 mg (mg/tablet)	% w/w	49 mg/ 51 mg (mg/tablet)	% w/w	97 mg/ 103 mg (mg/tablet)	% w/w	Maximum Levels (dosage per unit) (mg)	IIG Limit for Oral Route of Administration (mg)
Intragraanular									
Sacubitril and Valsartan**	Active ingredient	(b)(4)							
Microcrystalline Cellulose**	(b)(4)								
(b)(4) } USP-NF									
Crospovidone									
(b)(4) } USP-NF									
Croscarmellose Sodium									
(b)(4) } USP-NF									
Colloidal Silicon Dioxide									
(b)(4) } USP-NF									
Talc (b)(4) USP									
Magnesium Stearate (b)(4)									
(b)(4) } USP-NF									
(b)(4)									
Iron Oxide Red	(b)(4)								
Black Iron Oxide									
(b)(4)									
Iron Oxide Yellow	(b)(4)								
(b)(4)									

(b)(4)

Coated Tablet weight	103.000	100.00	206.000	100.00	412.000	100.00	-	-
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(b)(4)

RLD	Test Product
Microcrystalline Cellulose	Microcrystalline Cellulose
Crospovidone	Crospovidone
Low-substituted hydroxypropyl Cellulose	Croscarmellose sodium
Colloidal silicon dioxide	Colloidal silicon dioxide
Talc	Talc
Magnesium stearate	Magnesium stearate
(b)(4)	
Hypromellose	Hypromellose
Titanium dioxide	Titanium dioxide
Macrogol 4000	Macrogol/
(b)(4)	
Iron oxide red	Red iron oxide
Iron oxide Black	Black Iron oxide

(b)(4)

Iron oxide yellow

(b)(4)

(b)(4)

(b)(4)

RLD	Test Product
(b)(4)	

Assessment:

Adequate

Strength	Product Description
24 mg/ 26 mg	Purple colored, oval shaped, biconvex, film coated tablets one side debossed with 'M' and other side debossed with 'S1' (b)(4)
49 mg/51 mg	Light yellow to yellow colored, oval shaped, biconvex, film coated tablets one side debossed with 'M' and other side debossed with 'S2' (b)(4)
97 mg/ 103 mg	Light pink to pink colored, oval shaped, biconvex, film coated tablets one side debossed with 'M' and other side debossed with 'S3' (b)(4)

The firm provided adequate information regarding to components and composition of the drug product.

(b)(4)

There are some minor differences in compositions between the generic proposed formulation and the formulation of the reference product, but they should not have any effects on the quality of the drug products.

However, whether the difference between this proposed formulation and the RLD present any potential concerns with respect to therapeutic equivalence of drug product would rely on the evaluation of Division of Bioequivalence.

The size and shape of generic Sacubitril and Valsartan tablets meets the requirements as per "Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules" as shown in the table below.

DELETED PAGES INFORMATION SHEET

IT IS NOT REASONABLE TO SEGREGATE MEANINGFUL PORTIONS OF THE RECORD FOR RELEASE.

INFORMATION HAS BEEN WITHHELD IN ITS ENTIRETY IN ACCORDANCE WITH THE FOLLOWING EXEMPTIONS(S):

(b) (4)

5 U.S.C. 552 (b) (4) - trade secrets and commercial or financial information obtained from a person and privileged or confidential.

Methods Validation or Verification Package

Assessment:

Adequate

Comparability Protocols

Assessment:

N/A

Choose an item.

Lifecycle Management Considerations

DRUG PRODUCT LIST OF DEFICIENCIES)

N/A

CHAPTER III: ENVIRONMENTAL

R REGIONAL INFORMATION

Environmental

Assessment:

Adequate

CHAPTER IV: LABELING

R REGIONAL INFORMATION

1.14 Labeling

Labeling & Prescribing Information

DESCRIPTION (Rx insert or Active Ingredient(s), and Inactive Ingredients in DRUG FACTS for OTC):

Is the information accurate? ☒ Yes ☐ No

If "No," explain.

Is the drug product subject of a USP monograph? ☐ Yes ☒ No

If "Yes," does labeling have accurate USP statement in the DESCRIPTION (for Rx) or Other Information section of DRUG FACTS (for OTC)?

☐ Yes ☐ No ☐ Statement not needed

If NO, what is/are the needed statement(s)? _____

HOW SUPPLIED section (Rx insert) or Storage (in DRUG FACTS for OTC)

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Is tamper evident feature provided in the container/closure for the OTC products or Controlled Substance (CII – CIV) products? ☐ Yes ☐ No
☒ N/A (NOT OTC or Controlled Substance)

If "No," explain.

For solid oral drug products, only: drug product length(s) of commercial batch(es):

ANDA Strength	Length (MM)	Imprint Code
24 mg/ 26 mg	10.00 x 4.00	one side debossed with 'M' and other side debossed with 'S1'
49 mg/ 51 mg	13.00 x 5.10	one side debossed with 'M' and other side debossed with 'S2'
97 mg/ 103 mg	15.00 x 5.90	one side debossed with 'M' and other side debossed with 'S3'

Send issue to the Labeling assessor through the Platform with a list of quality-related labeling deficiencies and also record reference number or link for all the issues:

Issue Description	Issue Reference Number or Link

LABELING LIST OF DEFICIENCIES

N/A

ATTACHMENT II: List of All Deficiencies

N/A



Behnam
Abdolzadeh

Digitally signed by Behnam Abdolzadeh
Date: 8/09/2023 05:52:57AM
GUID: 51dc72810000c6e47569a654b09e35e0



Mayra
Pineiro Sanchez

Digitally signed by Mayra Pineiro Sanchez
Date: 8/08/2023 09:43:48PM
GUID: 508da702000288099b99e9faff8a6a27

RECOMMENDATION

☐ Approval
☐ Complete Response-Minor
☐ Complete Response-Minor + Travel Comment
☒ Complete Response-Major
☐ Complete Response-Major + Travel Comment
☐ Complete Response-Major-Facilities Only
☐ Complete Response-Deferred-Travel Restriction-COVID19 <i>Choose this option when both of the following apply:</i> • <i>Quality is Adequate except for inspection deferred due to travel restriction</i> <u>AND</u> • <i>OGD has deficiencies (e.g., Bioequivalence, Labeling, etc.)</i>

ANDA 213748 Assessment #R03

Drug Product Name	Sacubitril and Valsartan
Dosage Form	Tablets
Strength	24 mg/26 mg, 49 mg /51 mg and 97 mg/103 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	MSN Laboratories Private Limited
US agent, if applicable	MSN Pharmaceuticals Inc.

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original/Initial Submission	07/07/2019	All
Quality/Response to Discipline Review Letter	2/27/2020	Quality
Resubmission/After Action- Complete Response	08/19/2020	Quality
Quality/Response To Information Request	08/28/2020	Quality
CR Response	02/09/2022	Quality
IR response	02/23/2022	Quality

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Donglei YuErin Skoda Srinivasa Murthy	Erin Skoda Anita Tiwari
Drug Product	Behnam Abdolalizadeh	Mayra Pineiro-Sanchez
Manufacturing	Amit Kokate	Jean Tang
Microbiology	N/A	N/A
Biopharmaceutics	Ho-Pi Lin	N/A
Regulatory Business Process Manager	Candice Cottle-Delisle	
Application Technical Lead	Mayra Pineiro-Sanchez	
Laboratory (OTR)	N/A	N/A
Environmental	N/A	N/A

*If Active Pharmaceutical Ingredient (API) data is provided as part of ANDA submission, list Division of Lifecycle API (DLAPI) Assessor

QUALITY ASSESSMENT DATA SHEET

For more details about the items in this template, please see the [Quality Assessment Data Sheet chapter of the ANDA IQA Guide](#)

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Reviewed	Comments
(b)(4)	II	(b)(4)	Sacubitril and Valsartan	Adequate	04/07/2022	R04
	II			Adequate	02/14/2022	
	II			Adequate	04/05/2022	
	IV		(b)(4)			
	IV					
	IV					
	III					Refer to 3.2.P.7

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved ANDA*

Document	Application Number	Brand Name	Description
NDA	207620	ENTRESTO®	Sacubitril and Valsartan Tab, 24/26, 49 /51, 97 /103 mg

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH-ODE	N/A			
CDRH-OC	N/A			
Clinical	N/A			
Other	N/A			

ABBREVIATED EXECUTIVE SUMMARY (CR ONLY)

For more details about the items in this template, please see the [Abbreviated Executive Summary \(CR Only\) chapter of the ANDA IQA Guide](#)

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Complete Response-Major

The applicant has **NOT** provided sufficient information to assure the

(b)(4)

- DMF # [redacted] - AQ
- **Drug Substance – IQ Major** [redacted]
- **Drug Product – IQ Minor**
- OPMA – AQ
- Biopharmaceuticals - AQ

Therefore, from the quality perspective, this ANDA is **NOT** recommended for approval.

II. QUALITY ASSESSMENT OVERVIEW

III. A. DP OVERALL RECOMMENDATION: Inadequate-Major

Drug Substance: Inadequate-Major

1. Provide Justification, if **Major**: (Click link to view [Justification Statements](#))

The drug product deficiencies have been classified as MAJOR because new analytical methods are needed to assure product quality as noted in Appendix A, Section A(2)(i) of the guidance for industry ANDA Submissions – Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). Upon receipt, in FDA's judgement, the review of these methods will require substantial expenditure of FDA resources.

2. Insert additional **Major** justification below (if necessary)

(b)(4)

Drug Product: Inadequate-Minor

1. Provide Justification, if **Major**: (Click link to view [Justification Statements](#))

2. Insert additional **Major** justification below (if necessary)

Sacubitril and Valsartan Tablet is not a compendial item.

(b)(4)

(b)(4)

Labeling: Adequate

There is adequate quality information on the label.

Adequate data is provided in the ANDA to support preparation of oral suspension per labeling recommendations.

B. Manufacturing:**a. Process: Adequate**

1. Provide Justification, if **Major**: (Click link to view [Justification Statements](#))

2. Insert additional **Major** justification below (if necessary)

Summary:

(b)(4)

b. Facilities: Adequate

1. Provide Justification, if **Major**: (Click link to view [Justification Statements](#))

2. Insert additional **Major** justification below (if necessary)

Summary:

OMIR is approve 11APR2022

C. Biopharmaceutics: Adequate

1. Provide Justification, if **Major**: (Click link to view [Justification Statements](#))

2. Insert additional **Major** justification below (if necessary)

This ANDA 213748 is recommended for approval from a biopharmaceutics perspective.

USP Apparatus	Speed	Medium/Temperature	Acceptance criterion(a)
---------------	-------	--------------------	-------------------------

I (Basket)	75 rpm	pH 6.8 phosphate buffer/37°C 900 ml	Q= % in 20 minutes (Sacubitril & Valsartan)
------------	--------	--	--

D. Microbiology: N/A

1. Provide Justification, if **Major**: (Click link to view [Justification Statements](#))

2. Insert additional **Major** justification below (if necessary)

N/A

E. List of Deficiencies for Complete Response

Overall Quality Deficiencies - Optional (*Deficiencies that affect multiple sub-disciplines*)

Drug Substance Deficiencies

1.

(b)(4)

Drug Product Deficiencies

1.

(b)(4)

a.

b.

(b)(4)

(b)(4)

Labeling Deficiencies *(Please contact OGD if you identify any Labeling deficiencies with your comments)*

Manufacturing Deficiencies

Biopharmaceutics Deficiencies

Microbiology Deficiencies

Other Deficiencies *(Specify discipline, such as Environmental)*

In addition to responding to the deficiencies presented above, please note and acknowledge the following comment(s) in your response:

Application Technical Lead Name and Date: Mayra L. Pineiro-Sanchez,
4/26/2022



Mayra
Pineiro Sanchez

Digitally signed by Mayra Pineiro Sanchez
Date: 4/26/2022 09:33:07PM
GUID: 508da702000288099b99e9faff8a6a27

RECOMMENDATION

☒ Complete Response-Major
☐ Complete Response-Minor
☐ Discipline Review Letter (DRL)
☐ Information Request—IR x Days
☐ Approval

ANDA 213748 Assessment Cycle #020303

Drug Product Name	Sacubitril and Valsartan Tablets
USP Monograph	☐ Yes ☒ No
Strength	24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg
Dosage Form	Tablets
Route of Administration	Oral
Rx/OTC Dispensed	☒ Rx ☐ OTC
ANDA Applicant	MSN Laboratories Private Limited
Drug Product Manufacturer	☒ Same as the Applicant ☐ Different from the Applicant (see below)
US agent, if applicable	☐ N/A ☒ (See Below) MSN Pharmaceuticals Inc. 20 Duke Road, Piscataway, NJ 08854-3714
Proposed Indication	Sacubitril and Valsartan Tablets indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure () and reduced ejection fraction.

Submission(s) Assessed	Document Date	Discipline(s) Affected
CR 02	2/9/2022	Quality
CR 01	8/19/2020	Quality
Amendment-Response to DRL	2/27/2020	Quality
Original	7/8/2019	All
Labeling-Response to Discipline Review Letter*	10/30/2019	Labeling

*Preparation of oral suspension added in label to be in line with RLD, but no supporting quality information provided

Submission assessed CR 01 and CR 02 was assessed by B. Abdolalizadeh

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QUALITY ASSESMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Reviewed	Comments
(b)(4)	II	(b)(4)	Sacubitril and Valsartan	Adequate	04/07/2022	D. Yu
	II			Adequate	02/09/2022	D. Yu
	II		(b)(4)	Adequate	03/09/2021	S. Murthy
Other DMF: ☐ N/A ☒ (See Below)						
(b)(4)	III	(b)(4)				
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	IV					
	IV					
	IV					
	Other					
	(b)(4)					

B. OTHER DOCUMENTS: IND, RLD, RS, Approved ANDA

Document	Application Number	Brand Name	Description
NDA	207620	ENTRESTO®	Sacubitril and Valsartan Tab, 24/26, 49 /51, 97 /103 mg

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH-ODE	N/A			
CDRH-OC	N/A			
Clinical	N/A			
Other	N/A			

PART I. Review of Firm's Response to Deficiencies

Review of Amendment Dated 02/09/2022 (current review)

(b)(4)

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**OLDP Assessment Team: 1ry: Qiuxia Wang; QAL:
Raghu Samy**

CHAPTER I: DRUG SUBSTANCE

[IQA ANDA Assessment Guide Reference](#)

Drug Substance Name	Sacubitril and Valsartan
DMF Number (If Applicable)	(b)(4)
DMF Status	Adequate
DMF Holder	(b)(4)

Overall Assessment Recommendation for DS:

Adequate

Theme:

☐ N/A	☐ Other (Requires Division Director Approval)
☐ DMF	☐ Due to Consult
☐ New DS Batch	

Justification: view justification statements found at: [Justification Statements](#)

Paste appropriate justification statement(s) here or insert "N/A" if not applicable.
Other (Requires Division Director Approval)- Assessor writes justification here if "other" selected as theme.

Justification for Major from DMF review

An unqualified impurity (toxicology studies required to qualify the impurity): New toxicology studies are requested for the unqualified impurity and the review of these studies requires substantial expenditure of FDA resources and will potentially affects other aspects of the application and the related conclusions.

Highlight Key Issues from Last Cycle and Their Resolution:

No Key issues with DS from last cycle review

Concise Description of Outstanding Issues:

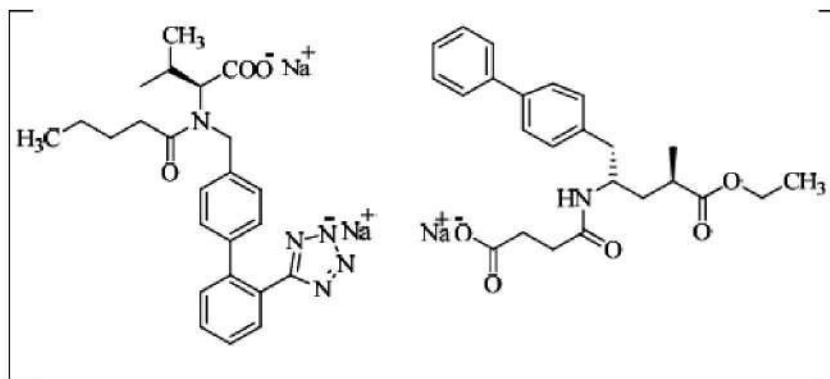
N/A - No Deficiencies with DS in the ANDA

Inadequate DMF-Major

Select Number of Approved Comparability Protocols: 00

S.1 GENERAL INFORMATION

Recommended International Nonproprietary Name	Sacubitril and Valsartan
USAN	Sacubitril and Valsartan
Chemical Name(s)	Tri sodium (4- {[(1 S,3R)-1-([1,1'-biphenyl] 4-ylmethyl)-4-ethoxy-3-methyl-4-oxobutyl]amino } -4-oxobutanoate)-(N-pentanoyl-N-{[2'-(1H-tetrazol-1-yl-5-yl)[1,1'-biphenyl]-4-yl]methyl }-L-valinate)
CAS Number	936623-90-4
Therapeutic Category	To treat heart failure
Structure	



Molecular Formula C₄₈H₅₅N₆O₈Na₃

Molecular Weight 912.96

Description White to almost white powder.

(b)(4)

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DRUG SUBSTANCE LIST OF DEFICIENCIES (from Review 1A):

(b)(4)

DRUG SUBSTANCE LIST OF DEFICIENCIES (from Review 1):

1.

2.

(b)(4)

CHAPTER II: DRUG PRODUCT

[IQA ANDA Assessment Guide Reference](#)

Overall Assessment Recommendation:

Inadequate - Major

Theme:

☒ N/A	☐ Unacceptable Analytical Methods
☐ Unqualified Impurity	☐ Application Quality
☐ New DP Batch	☐ Pharmaceutical Equivalence
☐ Product Design	☐ Product Safety
☐ Failing Stability Data	☐ Other (Requires Division Director Approval)
☐ Application Completeness	☐ Due to Consult

Justification: view justification statements found at: [Justification Statements](#)

Paste appropriate justification statement(s) here or insert "N/A" if not applicable.
Other (Requires Division Director Approval)- Assessor writes justification here if "other" selected as theme.

Assessment Summary:

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking After Assessment Cycle #	Comments

Note: This table will be updated in Executive Summary at time of approval.

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Concise Description of Outstanding Issues (*List Bullet Points with Key Information and Update as Needed*): see deficiency letter

Select Number of Approved Comparability Protocols: 0

List Current Quality Endorsement Status:

- USP monograph for Drug Product and compliance (current USP) – status: not USP
- Dissolution status: dissolution method and specifications are finalized with Biopharmaceutics. Applicant has not provided stability data per final specifications. Applicant will be asked to provide dissolution data with revised specifications to confirm shelf-life proposal

- Elemental impurity compliance with ICH Q3D – status: adequate
- Number of Comparability protocols included: 0

P.1 DESCRIPTION AND COMPOSITION

The quantitative composition and function of each excipient in the drug product is listed.

Ingredients	Functions	24 mg/ 26 mg (mg/tablet)	% w/w	49 mg/ 51 mg (mg/tablet)	% w/w	97 mg/ 103 mg (mg/tablet)	% w/w	Maximum Levels (dosage per unit) (mg)	IIG Limit for Oral Route of Administration (mg)
(b)(4)									
Sacubitril and Valsartan**	Active ingredient	(b)(4)							
Microcrystalline Cellulose** (b)(4) USP-NF	(b)(4)								
Crospovidone (b)(4) USP-NF									
Croscarmellose Sodium (b)(4) USP-NF									
Colloidal Silicon Dioxide (b)(4) USP-NF									
Talc (b)(4) USP									
Magnesium Stearate (b)(4) (b)(4) USP-NF									
(b)(4)									
(b)(4)									
Iron Oxide Red	(b)(4)								
Black Iron Oxide									
(b)(4)									
Iron Oxide Yellow	(b)(4)								
(b)(4)									

Ingredients	Functions	24 mg/ 26 mg (mg/tablet)	% w/w	49 mg/ 51 mg (mg/tablet)	% w/w	97 mg/ 103 mg (mg/tablet)	% w/w	Maximum Levels (dosage per unit) (mg)	IIG Limit for Oral Route of Administration (mg)
(b)(4)									
Coated Tablet weight		103.000	100.00	206.000	100.00	412.000	100.00	-	-

(b)(4)

RLD	Test Product
Microcrystalline Cellulose	Microcrystalline Cellulose (b)(4)
Crospovidone	Crospovidone – (b)(4)
Low-substituted hydroxypropyl Cellulose	Croscarmellose sodium
Colloidal silicon dioxide	Colloidal silicon dioxide
Talc	Talc (b)(4)
Magnesium stearate	Magnesium stearate
(b)(4)	
Hypromellose	Hypromellose
Titanium dioxide	Titanium dioxide
Macrogol 4000	Macrogol (b)(4)
(b)(4)	
Iron oxide red	Red iron oxide (b)(4)
Iron oxide Black	Black Iron oxide (b)(4)
(b)(4)	
(b)(4)	(b)(4)
Iron oxide yellow	
(b)(4)	
(b)(4)	

RLD	Test Product
(b)(4)	

Assessment:

Adequate

Strength	Product Description
24 mg/ 26 mg	Purple colored, oval shaped, biconvex, film coated tablets one side debossed with 'M' and other side debossed with 'S1' (b)(4)
49 mg/51 mg	Light yellow to yellow colored, oval shaped, biconvex, film coated tablets one side debossed with 'M' and other side debossed with 'S2' (b)(4)
97 mg/ 103 mg	Light pink to pink colored, oval shaped, biconvex, film coated tablets one side debossed with 'M' and other side debossed with 'S3' (b)(4)

The firm provided adequate information regarding to components and composition of the drug product.

(b)(4)

There are some minor differences in compositions between the generic proposed formulation and the formulation of the reference product, but they should not have any effects on the quality of the drug products.

However, whether the difference between this proposed formulation and the RLD present any potential concerns with respect to therapeutic equivalence of drug product would rely on the evaluation of Division of Bioequivalence.

The size and shape of generic Sacubitril and Valsartan tablets meets the requirements as per "Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules" as shown in the table below.

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(b) (4)

5 U.S.C. 552 (b) (4) - trade secrets and commercial or financial information obtained from a person and privileged or confidential.

Methods Validation or Verification Package

Assessment:

Adequate

Comparability Protocols

Assessment:

N/A

Choose an item.

Lifecycle Management Considerations

DRUG PRODUCT LIST OF DEFICIENCIES (from Review 1A)

1.	(b)(4)
2.	
3.	

DRUG PRODUCT LIST OF DEFICIENCIES (from Review 1)

1.	(b)(4)
----	---

DELETED PAGES INFORMATION SHEET

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CHAPTER III: ENVIRONMENTAL

R REGIONAL INFORMATION

Environmental

Assessment:

Adequate

CHAPTER IV: LABELING

R REGIONAL INFORMATION

1.14 Labeling

Labeling & Prescribing Information

DESCRIPTION (Rx insert or Active Ingredient(s), and Inactive Ingredients in DRUG FACTS for OTC):

Is the information accurate? ☒ Yes ☐ No

If "No," explain.

Is the drug product subject of a USP monograph? ☐ Yes ☒ No

If "Yes," does labeling have accurate USP statement in the DESCRIPTION (for Rx) or Other Information section of DRUG FACTS (for OTC)?

☐ Yes ☐ No ☐ Statement not needed

If NO, what is/are the needed statement(s)? _____

HOW SUPPLIED section (Rx insert) or Storage (in DRUG FACTS for OTC)

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Is tamper evident feature provided in the container/closure for the OTC products or Controlled Substance (CII – CIV) products? ☐ Yes ☐ No
☒ N/A (NOT OTC or Controlled Substance)

If "No," explain.

For solid oral drug products, only: drug product length(s) of commercial batch(es):

ANDA Strength	Length (MM)	Imprint Code
24 mg/ 26 mg	10.00 x 4.00	one side debossed with 'M' and other side debossed with 'S1'
49 mg/ 51 mg	13.00 x 5.10	one side debossed with 'M' and other side debossed with 'S2'
97 mg/ 103 mg	15.00 x 5.90	one side debossed with 'M' and other side debossed with 'S3'

Send issue to the Labeling assessor through the Platform with a list of quality-related labeling deficiencies and also record reference number or link for all the issues:

Issue Description	Issue Reference Number or Link

LABELING LIST OF DEFICIENCIES

None

ATTACHMENT II: List of All Deficiencies (from Review Cycle #2)

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(b) (4)

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(b)(4)

A. Labeling Deficiencies

None

(END OF DRUG PRODUCT QUALITY ASSESSMENT)

Concur with deficiencies

Signature Block (Review 1):

Primary DP Assessor:	<u>Qiuxia Wang</u>	Date:	<u>10/31/2019,</u> <u>12/18/19</u>
Secondary DP Assessor:	<u>Raghu Samy</u>	Date:	<u>11/22/19,</u> <u>12/18/19</u>

Signature Block (Review 1A):

Concur with deficiencies

Primary DP Assessor:	<u>Qiuxia Wang</u>	Date:	<u>3/19/2020,</u> <u>5/28/2020</u>
Secondary DP Assessor:	<u>Raghu Samy</u>	Date:	<u>4/7/2020,</u> <u>5/28/2020</u>



Behnam
Abdolzadeh

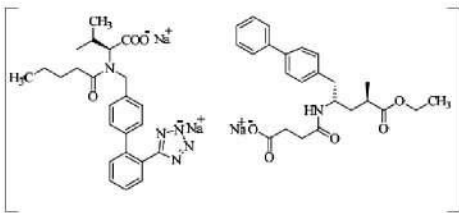
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Mayra
Pineiro Sanchez

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MANUFACTURING INTEGRATED ASSESSMENT

Application ID	ANDA 213748
Drug Product Name	Sacubitril and Valsartan Tablets  CAS #: 936623-90-4 Molecular Formula: C ₄₈ H ₅₅ N ₆ O ₈ Na ₃ Molecular Weight: 912.96 g/mol Prioritization Factor: First Generic - Granted
Strengths	24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg
Dosage Form	Tablet
Administration Route	Oral
Indication	Sacubitril and valsartan tablet is indicated 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.
Applicant Name	MSN Laboratories Private Limited
RLD Number	N207620 ENTRESTO

Reviewer's Note:

Blue font refers to the current Amendment-12 (SD#12 received 02/09/2022)/review cycle

Black font refers to the previous review cycle (SD#9 received 08/28/2021)

I. Manufacturing Summary

Facility Assessment Recommendation: Adequate

Process Assessment Recommendation: Adequate

Assessment Summary: The proposed drug product, Sacubitril and Valsartan Tablets, includes the same three dosage strengths as RLD, 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg, which are dose-weight proportional. (b)(4)

(b)(4)

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(b) (4)

5 U.S.C. 552 (b) (4) - trade secrets and commercial or financial information obtained from a person and privileged or confidential.

Document Description (SD #)	Date Received
Original Submission, Seq. 0000 (1)	07/08/2019
CMC Amendment (Response to DRL), Seq. 0005 (6)	02/27/2020
CMC Amendment (Response to CRL), Seq. 0007 (8); Amend-8	08/19/2020
CMC Amendment (Response to IR), Seq. 0008 (9)	08/28/2020
CMC Amendment (Response to CRL), Seq. 0011 (12)	02/09/2022
CMC Amendment (Response to IR), Seq. 0012 (13)	02/23/2022

Note: Seq. 0001 (2), 0002 (3), 0003 (4), 0004 (5), 0006 (7), 0009 (10), 0010(11) are not CMC related submissions.

Highlight Key Issues from Last Cycle and Their Resolution: See CR#1

-
-

(b)(4)

Concise Description of Outstanding Issues (List bullet points with key information and update as needed): N/A

List Number of Comparability Protocols: None

1. Lifecycle Management Considerations

Post-approval inspection?	No
Lifecycle considerations	No

2. Facilities Table

Facility name and address	FEI	Responsibilities and profile code(s)	Status
MSN Laboratories Private Limited Formulations Division, Unit-II, Survey No. 1277 & 1319 to 1324, Nandigama (Village), Nandigama (Mandal), Rangareddy District, Telangana, INDIA, 509228	3011033544	(b)(4)	Approve - Based on Previous History
MSN Life sciences Private Limited Unit-II, Sy.No. 455/A,455/AA,455/E and 455/EE Chandampet (Village), Shankarampet-R (Mandal), Medak District, Telangana, INDIA, 502255	3011543392		Approve - Based on PAI

MSN Laboratories Private Limited (Research & Development)	3005075182	(b)(4)	No Evaluation Necessary
Plot No. 12, Phase-IV, Sy.No. 119 to 140, 258, 275 to 280, Industria Park, Pashamylaram (Village), Patancheru (Mandal), Sanga reddy district, Telangana, INDIA, 502307			
MSN Laboratories Private Limited	3005254981		Approve - Based on Previous History
Sy. No. 317 & 320, 321, 322,323, 604 & 605, Rudraram (Village), Patancheru (Mandal), Sangareddy District, Telangana, India, 502329			
(b)(4)			
MSN Pharmachem Private Limited	3006165229	(b)(4)	Approve - Based on Previous History
Plot No.: 212/ A,B,C,D, Phase-II, IDA Pashamylaram, Pashamylaram (Village), Patancheru (Mandal), , Sangareddy District,, Telangana,, India, 502 307			

Update (Amendment-8):

(b)(4)

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II.

(b)(4)

Manufacturing

1. Batch Formula

Ingredients	Functions	24 mg/ 26 mg (mg/tablet)	49 mg/ 51 mg (mg/tablet)	97 mg/ 103 mg (mg/tablet)
Intrgranular				
Sacubitril and Valsartan	API			
Microcrystalline Cellulose (b)(4) USP-NF#				
Crospovidone (b)(4) USP-NF				
Croscarmellose Sodium (b)(4) SP-NF				
Colloidal Silicon Dioxide USP-NF				
Talc (b)(4) USP				
Magnesium Stearate (b)(4) USP-NF				
(b)(4)	(b)(4)			
Total tablet weight		103.000	206.000	412.000

(b)(4)

(b)(4)

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(b) (4)

5 U.S.C. 552 (b) (4) - trade secrets and commercial or financial information obtained from a person and privileged or confidential.

VI. Signature Block

Round#	Primary Name	Secondary & Other Names	Date of Completion	Assessment Outcome	Facility OMIR
1	Jingbo Xiao 09/03/2019 11/22/2019 12/16/2019	Vaikunth S. Prabhu 09/05/2019 12/12/2019 12/17/2019	12/17/2019	IR	TBD
2	Jingbo Xiao 03/04/2020 04/07/2020 05/27/2020	Vaikunth S. Prabhu 03/19/2020 04/07/2020 05/27/2020	5/27/2020	CR Major	Withheld
3	Amit Kokate 1/25/2021	Jean Tang 2/1/2021	3/15/2021	CR Minor	Approve
4	Amit Kokate	Jean Tang	3/29/2022	Adequate	Approve



Amit
Kokate

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Jean
Tang

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ANDA 213748

INFORMATION REQUEST

Dr. Kondal Reddy Bairy
U.S. Agent for MSN Laboratories Private Limited
MSN Pharmaceuticals Inc.
20 Duke Road
Piscataway, NJ 08854-3714

Dear Dr. Kondal Reddy Bairy:

This letter is in reference to your approved abbreviated new drug application (ANDA) submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Sacubitril and Valsartan Tablets, 24 mg/26 mg, 49 mg /51 mg and 97 mg/103 mg.

(b)(4)

FDA's assessment of your application will include an evaluation of the concerns detailed in this Information Request letter during the next assessment cycle. Please submit your response to this Information Request letter with your next submission. If you have already addressed this request, please cross-reference where this is submitted to your application in your response.

¹ ICH M7(R1): Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk

If you have any questions, please email Elisa Nickum, Regulatory Business Process Manager, at elisa.nickum@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Vilayat A. Sayeed, Ph.D.
Director
Division of IR and MR Product 1
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

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Vilayat
Sayeed

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Date: 1/11/2022 01:26:26PM
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RECOMMENDATION

☐ Approval
☒ Complete Response-Minor
☐ Complete Response-Major
☐ Complete Response-Major-Facilities Only

ANDA 213748 Assessment #2

Drug Product Name	Sacubitril and Valsartan
Dosage Form	Tablets
Strength	24 mg/26 mg, 49 mg /51 mg and 97 mg/103 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	MSN Laboratories Private Limited
US agent, if applicable	MSN Pharmaceuticals Inc.

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original/Initial Submission	07/07/2019	All
Quality/Response to Discipline Review Letter	2/27/2020	Quality
Resubmission/After Action- Complete Response	08/19/2020	Quality
Quality/Response To Information Request	08/28/2020	Quality

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Donglei YuErin Skoda Srinivasa Murthy	Erin Skoda Anita Tiwari
Drug Product	Behnam Abdolalizadeh	Mayra Pineiro-Sanchez
Manufacturing	Amit Kokate	Jean Tang
Microbiology	N/A	N/A
Biopharmaceutics	Ho-Pi Lin	N/A
Regulatory Business Process Manager	Candice Cottle-Delisle	
Application Technical Lead	Mayra Pineiro-Sanchez	
Laboratory (OTR)	N/A	N/A
Environmental	N/A	N/A

QUALITY ASSESMENT DATA SHEET

[IQA ANDA Assessment Guide Reference](#)

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Reviewed	Comments
(b)(4)	II	(b)(4)	Sacubitril and Valsartan	Inadequate	03/12/2021	D. Yu
	II		(b)(4)	Inadequate	03/11/2021	D. Yu
	II			Adequate	03/09/2021	S. Murthy
Other DMF: ☐ N/A ☒ (See Below)						
(b)(4)	III	(b)(4)				
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	IV					
	IV					
	IV					
	Other					

*DMF was reviewed by D. Yu on 05/13/2020 and status was inadequate per review #2.

**Supporting DMF for DMF 033398

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved ANDA*

Document	Application Number	Brand Name	Description
NDA	207620	ENTRESTO®	Sacubitril and Valsartan Tab, 24/26, 49 /51, 97 /103 mg

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH-ODE	N/A			
CDRH-OC	N/A			

Clinical	N/A			
Other	N/A			

ABBREVIATED EXECUTIVE SUMMARY (CR ONLY)

[IQA ANDA Assessment Guide Reference](#)

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Minor

*The applicant has **NOT** provided sufficient information to assure the identity, strength, purity, and quality of the drug product during the expiration dating period of 24 months.*

- **DMF** (b)(4) - **IQ**
- **Drug Substance – IQ (DMF only)**
- **Drug Product – IQ Minor**
- **OPMA – IQ Minor**
- **Biopharmaceuticals - AQ**

*Therefore, from the quality perspective, this ANDA is **NOT** recommended for approval.*

II. QUALITY ASSESSMENT OVERVIEW

A. Drug Substance: Inadequate-Minor

1. Primary Justification:

2. Secondary Justification (if necessary):

3. Tertiary Justification (if necessary):

4. Insert additional justification below (if necessary)

DMF # 033398 for Sacubitril and Valsartan held by MSN Life Sciences Private Limited is inadequate

Drug Product: Inadequate-Minor

1. Primary Justification:

2. Secondary Justification (if necessary):

3. Tertiary Justification (if necessary):

4. Insert additional justification below (if necessary)

The drug product is an immediate release tablet and non-compendial. A deficiency related to limits for assay is identified this cycle.

Labeling: Adequate

The labeling section was adequate based on review of information provided in the original submission.

B. Manufacturing: Inadequate-Minor

1. Primary Justification:

2. Secondary Justification (if necessary)

3. Tertiary Justification (if necessary):

4. Insert additional justification below (if necessary)

(b)(4)

(b)(4)

C. Biopharmaceutics: Adequate

1. Primary Justification:

2. Secondary Justification (if necessary):

3. Tertiary Justification (if necessary):

4. Insert additional justification below (if necessary)

This ANDA 213748 is recommended for approval from a biopharmaceutics perspective.

USP Apparatus	Speed	Medium/Temperature	Acceptance criterion(a)
I (Basket)	75 rpm	pH 6.8 phosphate buffer/37°C 900 ml	Q= % in 20 minutes (Sacubitril & Valsartan)

D. Microbiology: Choose an item.

1. Primary Justification:

N/A

2. Secondary Justification (if necessary):

3. Tertiary Justification (if necessary):

4. Insert additional justification below (if necessary)

N/A

E. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies - Optional (Deficiencies that affect multiple sub-disciplines)

None

2. Drug Substance Deficiencies

1.

(b)(4)

3. Drug Product Deficiencies

1.

(b)(4)

4. Labeling Deficiencies (Please contact OGD if you identify any Labeling deficiencies with your comments)

None

5. Manufacturing Deficiencies

1.

(b)(4)

(b)(4)

6. Biopharmaceutics Deficiencies

None

7. Microbiology Deficiencies

N/A

8. Other Deficiencies (Specify discipline, such as Environmental)

N/A

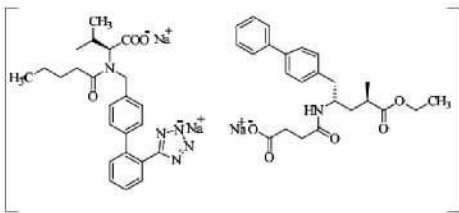
Application Technical Lead Name and Date: Mayra L. Pineiro-Sanchez



Mayra
Pineiro Sanchez

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MANUFACTURING INTEGRATED ASSESSMENT

Application ID	ANDA 213748
Drug Product Name	Sacubitril and Valsartan Tablets  CAS #: 936623-90-4 Molecular Formula: C ₄₈ H ₅₅ N ₆ O ₈ Na ₃ Molecular Weight: 912.96 g/mol Prioritization Factor: First Generic - Granted
Strengths	24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg
Dosage Form	Tablet
Administration Route	Oral
Indication	Sacubitril and valsartan tablet is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (b)(4) and reduced ejection fraction.
Applicant Name	MSN Laboratories Private Limited
RLD Number	N207620 ENTRESTO

Reviewer's Note:

Blue font refers to the current Amendment-8 (received 08/19/2020)/review cycle

Black font refers to the previous review cycle (Seq 0005; SD#6)

I. Manufacturing Summary

Facility Assessment Recommendation: Adequate

Process Assessment Recommendation: Inadequate - Minor

Assessment Summary: The proposed drug product, Sacubitril and Valsartan Tablets, includes the same three dosage strengths as RLD, 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg, which are dose-weight proportional. (b)(4)

(b)(4)

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5 U.S.C. 552 (b) (4) - trade secrets and commercial or financial information obtained from a person and privileged or confidential.

Highlight Key Issues from Last Cycle and Their Resolution: See CR#1

-
-
-

(b)(4)

Concise Description of Outstanding Issues (List bullet points with key information and update as needed): [Inadequate in-process specification for the final blend.](#)

List Number of Comparability Protocols: None

1. Lifecycle Management Considerations

Post-approval inspection?	No
Lifecycle considerations	No

2. Facilities Table

Facility name and address	FEI	Responsibilities and profile code(s)	Status
MSN Laboratories Private Limited Formulations Division, Unit-II, Survey No. 1277 & 1319 to 1324, Nandigama (Village), Nandigama (Mandal), Rangareddy District, Telangana, INDIA, 509228	3011033544	(b)(4)	Approve - Based on Previous History
MSN Life sciences Private Limited Unit-II, Sy.No. 455/A,455/AA,455/E and 455/EE Chandampet (Village), Shankarampet-R (Mandal), Medak District, Telangana, INDIA, 502255	3011543392		Approve - Based on PAI
MSN Laboratories Private Limited (Research & Development) Plot No. 12, Phase-IV, Sy.No. 119 to 140, 258, 275 to 280, Industria Park, Pashamylaram (Village), Patancheru (Mandal), Sanga reddy district, Telangana, INDIA, 502307	3005075182		No Evaluation Necessary
MSN Laboratories Private Limited Sy. No. 317 & 320, 321, 322,323, 604 & 605, Rudraram (Village),	3005254981		Approve - Based on Previous History

Patancheru (Mandal), Sangareddy District, Telangana, India, 502329			
(b)(4)			
MSN Pharmachem Private Limited Plot No.: 212/ A,B,C,D, Phase-II, IDA Pashamylaram, Pashamylaram (Village), Patancheru (Mandal), , Sangareddy District,, Telangana,, India, 502 307	3006165229	(b)(4)	Approve - Based on Previous History

Update (Amendment-8):

(b)(4)

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II. Drug Product Manufacturing

1. Batch Formula

Ingredients	Functions	24 mg/ 26 mg (mg/tablet)	49 mg/ 51 mg (mg/tablet)	97 mg/ 103 mg (mg/tablet)
Intrgranular				
Sacubitril and Valsartan	API			
Microcrystalline Cellulose USP-NF#				
Crospovidone USP-NF				
Croscarmellose Sodium USP-NF				
Colloidal Silicon Dioxide USP-NF				
Talc USP				
Magnesium Stearate USP-NF				
(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)
Total tablet weight		103.000	206.000	412.000
			(b)(4)	

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(b)(4)

VI. Signature Block

Round#	Primary Name	Secondary & Other Names	Date of Completion	Assessment Outcome	Facility OMIR
1	Jingbo Xiao 09/03/2019 11/22/2019 12/16/2019	Vaikunth S. Prabhu 09/05/2019 12/12/2019 12/17/2019	12/17/2019	IR	TBD
2	Jingbo Xiao 03/04/2020 04/07/2020 05/27/2020	Vaikunth S. Prabhu 03/19/2020 04/07/2020 05/27/2020	5/27/2020	CR Major	Withheld
3	Amit Kokate 1/25/2021	Jean Tang 2/1/2021	3/15/2021	CR Minor	Approve



Amit
Kokate

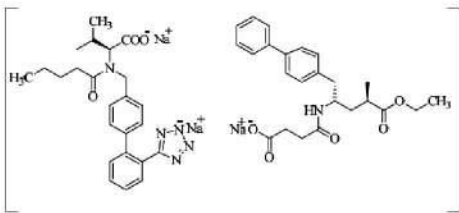
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Date: 3/16/2021 10:31:52AM
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Jean
Tang

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MANUFACTURING INTEGRATED ASSESSMENT

Application ID	ANDA 213748
Drug Product Name	Sacubitril and Valsartan Tablets  CAS #: 936623-90-4 Molecular Formula: C ₄₈ H ₅₅ N ₆ O ₈ Na ₃ Molecular Weight: 912.96 g/mol Prioritization Factor: First Generic - Granted
Strengths	24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg
Dosage Form	Tablet
Administration Route	Oral
Indication	Sacubitril and valsartan tablet is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (b)(4) and reduced ejection fraction.
Applicant Name	MSN Laboratories Private Limited
RLD Number	N207620 ENSTRESTO

I. Manufacturing Summary

Facility Assessment Recommendation: Inadequate - Major

THEME: Lack of Critical Facility

JUSTIFICATION: The facilities deficiencies have been classified as MAJOR because your submission failed to identify facilities required to be listed in the application as noted in Appendix A, Section A(6)(b) of the Guidance for Industry, ANDA Submissions - Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). Upon receipt, in FDA's judgement, the evaluation of new facilities added in an amendment and any additional inspections will require substantial expenditure of FDA resources.

Process Assessment Recommendation: Inadequate - Minor

Assessment Summary: The proposed drug product, Sacubitril and Valsartan Tablets, includes the same three dosage strengths as RLD, 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg, which are dose-weight proportional. (b)(4)

(b)(4)

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(b)(4)

List Number of Comparability Protocols: None

1. Lifecycle Management Considerations

Post-approval inspection?	No
Lifecycle considerations	No

2. Facilities Table

Facility name and address	FEI	Responsibilities and profile code(s)	Status
MSN Laboratories Private Limited Formulations Division, Unit-II, Survey No. 1277 & 1319 to 1324, Nandigama (Village), Nandigama (Mandal), Rangareddy District, Telangana, INDIA, 509228	3011033544	(b)(4)	Approve - Based on Previous History
MSN Life sciences Private Limited Unit-II, Sy.No. 455/A,455/AA,455/E and 455/EE Chandampet (Village), Shankarampet-R (Mandal), Medak District, Telangana, INDIA, 502255	3011543392		Approve - Based on PAI
MSN Laboratories Private Limited (Research & Development) Plot No. 12, Phase-IV, Sy.No. 119 to 140, 258, 275 to 280, Industria Park, Pashamylaram (Village), Patancheru (Mandal), Sanga reddy district, Telangana, INDIA, 502307	3005075182		No Evaluation Necessary
MSN Laboratories Private Limited Sy. No. 317 & 320, 321, 322,323, 604 & 605, Rudraram (Village), Patancheru (Mandal), Sangareddy District, Telangana, India, 502329	3005254981		Approve - Based on Previous History

(b)(4)

II. Drug Product Manufacturing

1. Batch Formula

Ingredients	Functions	24 mg/ 26 mg (mg/tablet)	49 mg/ 51 mg (mg/tablet)	97 mg/ 103 mg (mg/tablet)
Intrgranular				
Sacubitril and Valsartan	API			
Microcrystalline Cellulose (b)(4) USP-NF#				
Crospovidone (b)(4) USP-NF				
Croscarmellose Sodium (b)(4) SP-NF				
Colloidal Silicon Dioxide USP-NF				
Talc (b)(4) USP				
Magnesium Stearate (b)(4) USP-NF				
(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)
Total tablet weight		103.000	206.000	412.000

(b)(4)

(b)(4)

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1.

2.

(b)(4)

VI. Signature Block

Round#	Primary Name	Secondary & Other Names	Date of Completion	Assessment Outcome	Facility OMIR
1	Jingbo Xiao 09/03/2019 11/22/2019 12/16/2019	Vaikunth S. Prabhu 09/05/2019 12/12/2019 12/17/2019	12/17/2019	IR	TBD
2	Jingbo Xiao 03/04/2020 04/07/2020 05/27/2020	Vaikunth S. Prabhu 03/19/2020 04/07/2020 05/27/2020	5/27/2020	CR Major	(b)(4)



Jingbo
Xiao

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Vaikunth
Prabhu

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RECOMMENDATION

☐ Complete Response-Major
☒ Complete Response-Minor
☐ Discipline Review Letter (DRL)
☐ Information Request—IR x Days
☐ Approval

ANDA 213748 Assessment Cycle # 02

Drug Product Name	Sacubitril and Valsartan Tablets
USP Monograph	☐ Yes ☒ No
Strength	24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg
Dosage Form	Tablets
Route of Administration	Oral
Rx/OTC Dispensed	☒ Rx ☐ OTC
ANDA Applicant	MSN Laboratories Private Limited
Drug Product Manufacturer	☒ Same as the Applicant ☐ Different from the Applicant (see below)
US agent, if applicable	☐ N/A ☒ (See Below) MSN Pharmaceuticals Inc. 20 Duke Road, Piscataway, NJ 08854-3714
Proposed Indication	Sacubitril and Valsartan Tablets indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (b)(4) and reduced ejection fraction.

Submission(s) Assessed	Document Date	Discipline(s) Affected
CR 01	8/19/2020	Quality
Amendment-Response to DRL	2/27/2020	Quality
Original	7/8/2019	All
Labeling-Response to Discipline Review Letter*	10/30/2019	Labeling

*Preparation of oral suspension added in label to be in line with RLD, but no supporting quality information provided

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QUALITY ASSESMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Reviewed	Comments
(b)(4)	II	MSN Life Sciences Private Limited, Unit - II	Sacubitril and Valsartan	Inadequate	03/12/2021	D. Yu
	II			Inadequate	03/11/2021	D. Yu
	II		(b)(4)	Adequate	03/09/2021	S. Murthy
Other DMF: ☐ N/A ☒ (See Below)						
(b)(4)	III	(b)(4)				
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	IV					
	IV					
	IV					
	Other					
	(b)(4)					

B. OTHER DOCUMENTS: IND, RLD, RS, Approved ANDA

Document	Application Number	Brand Name	Description
NDA	207620	ENTRESTO®	Sacubitril and Valsartan Tab, 24/26, 49 /51, 97 /103 mg

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH-ODE	N/A			
CDRH-OC	N/A			
Clinical	N/A			

Other	N/A			
-------	-----	--	--	--

PART I. Review of Firm's Response to Deficiencies

Review of Amendment Dated 08/19/2020 (current review)

OLDP Assessment Team: Iry: Behnam Abdolalizadeh; SPQA: Mayra L. Pineiro-Sanchez

This amendment is in response to Complete Response Letter was issued by the agency on June 08, 2020.

Drug substance

Deficiency:

Issued on June 08, 2020

(b)(4)

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IT IS NOT REASONABLE TO SEGREGATE MEANINGFUL PORTIONS OF THE RECORD FOR RELEASE.

INFORMATION HAS BEEN WITHHELD IN ITS ENTIRETY IN ACCORDANCE WITH THE FOLLOWING EXEMPTIONS(S):

(b) (4)

5 U.S.C. 552 (b) (4) - trade secrets and commercial or financial information obtained from a person and privileged or confidential.

**OLDP Assessment Team: 1ry: Qiuxia Wang; QAL:
Raghu Samy**

CHAPTER I: DRUG SUBSTANCE

[IQA ANDA Assessment Guide Reference](#)

Drug Substance Name	Sacubitril and Valsartan
DMF Number (If Applicable)	(b)(4)
DMF Status	New DMF - Pending Review
DMF Holder	(b)(4)

Overall Assessment Recommendation for DS: **Inadequate - Major**

Theme:

☐ N/A	☐ Other (Requires Division Director Approval)
☒ DMF	☐ Due to Consult
☐ New DS Batch	

Justification: view justification statements found at: [Justification Statements](#)

Paste appropriate justification statement(s) here or insert "N/A" if not applicable.
Other (Requires Division Director Approval)- Assessor writes justification here if "other" selected as theme.

Justification for Major from DMF review

An unqualified impurity (toxicology studies required to qualify the impurity): New toxicology studies are requested for the unqualified impurity and the review of these studies requires substantial expenditure of FDA resources and will potentially affects other aspects of the application and the related conclusions.

Highlight Key Issues from Last Cycle and Their Resolution:

No Key issues with DS from last cycle review

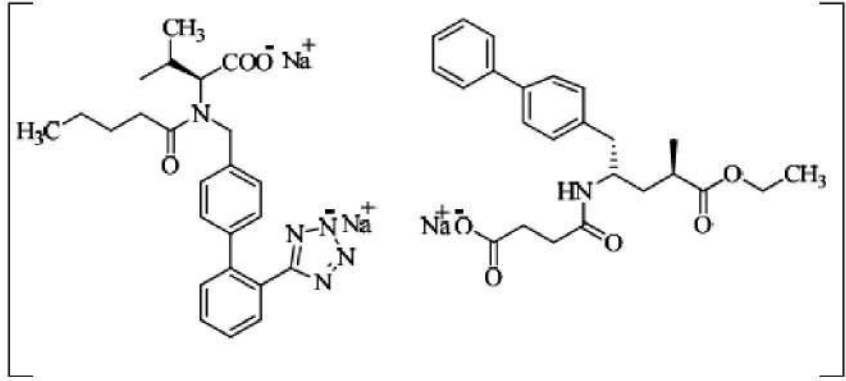
Concise Description of Outstanding Issues:

Below is a brief description of outstanding issues with DS in ANDA:

Inadequate DMF-Major

Select Number of Approved Comparability Protocols: 0

S.1 GENERAL INFORMATION

Recommended International Nonproprietary Name	Sacubitril and Valsartan
USAN	Sacubitril and Valsartan
Chemical Name(s)	Tri sodium (4-{[(1 S,3R)-1-([1,1'-biphenyl] 4-yl)methyl)-4-ethoxy-3-methyl-4-oxobutyl]amino}-4-oxobutanoate)-(N-pentanoyl-N-{[2'-(1H-tetrazol-1-yl)-5-yl][1,1'-biphenyl]-4-yl]methyl}-L-valinate)
CAS Number	936623-90-4
Therapeutic Category	To treat heart failure
Structure	
Molecular Formula	C ₄₈ H ₅₅ N ₆ O ₈ Na ₃
Molecular Weight	912.96

Description White to almost white powder.

(b)(4)

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DRUG SUBSTANCE LIST OF DEFICIENCIES (from Review 1A):

(b)(4)

DRUG SUBSTANCE LIST OF DEFICIENCIES (from Review 1):

1.

2.

(b)(4)

CHAPTER II: DRUG PRODUCT

IQA ANDA Assessment Guide Reference

Overall Assessment Recommendation:

Inadequate - Minor

Theme:

☒ N/A	☐ Unacceptable Analytical Methods
☐ Unqualified Impurity	☐ Application Quality
☐ New DP Batch	☐ Pharmaceutical Equivalence
☐ Product Design	☐ Product Safety
☐ Failing Stability Data	☐ Other (Requires Division Director Approval)
☐ Application Completeness	☐ Due to Consult

Justification: view justification statements found at: [Justification Statements](#)

Paste appropriate justification statement(s) here or insert "N/A" if not applicable.
Other (Requires Division Director Approval)- Assessor writes justification here if "other" selected as theme.

Assessment Summary:

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking After Assessment Cycle #	Comments

Note: This table will be updated in Executive Summary at time of approval.

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Concise Description of Outstanding Issues (List Bullet Points with Key Information and Update as Needed): see deficiency letter

Select Number of Approved Comparability Protocols: 0

List Current Quality Endorsement Status:

- USP monograph for Drug Product and compliance (current USP) – status: not USP
- Dissolution status: specifications are not finalized with Biopharmaceuticals, and implemented, and stability data complies with revised specifications (if applicable) to confirm shelf life proposal

- Elemental impurity compliance with ICH Q3D – status: adequate
- Number of Comparability protocols included: 0

P.1 DESCRIPTION AND COMPOSITION

The quantitative composition and function of each excipient in the drug product is listed.

Ingredients	Functions	24 mg/ 26 mg (mg/tablet)	% w/w	49 mg/ 51 mg (mg/tablet)	% w/w	97 mg/ 103 mg (mg/tablet)	% w/w	Maximum Levels (dosage per unit) (mg)	IIG Limit for Oral Route of Administration (mg)
Intraganular									
Sacubitril and Valsartan	Active ingredient	(b)(4)							
Microcrystalline Cellulose (b)(4) USP-NF	(b)(4)	(b)(4)							
Crospovidone (b)(4) USP-NF									
Croscarmellose Sodium (b)(4) USP-NF									
Colloidal Silicon Dioxide (b)(4) USP-NF									
Talc (b)(4) USP									
Magnesium Stearate (b)(4) USP-NF									
(b)(4)									
(b)(4)									
Iron Oxide Red	(b)(4)								
Black Iron Oxide									
(b)(4)									
Iron Oxide Yellow	(b)(4)								
(b)(4)									

Ingredients	Functions	24 mg/ 26 mg (mg/tablet)	% w/w	49 mg/ 51 mg (mg/tablet)	% w/w	97 mg/ 103 mg (mg/tablet)	% w/w	Maximum Levels (dosage per unit) (mg)	IIG Limit for Oral Route of Administration (mg)
(b)(4)									
Coated Tablet weight		103.000	100.00	206.000	100.00	412.000	100.00	-	-

(b)(4)

RLD	Test Product
Microcrystalline Cellulose	Microcrystalline Cellulose (b)(4)
Crospovidone	Crospovidone - (b)(4)
Low-substituted hydroxypropyl Cellulose	Croscarmellose sodium
Colloidal silicon dioxide	Colloidal silicon dioxide
Talc	Talc (b)(4)
Magnesium stearate	Magnesium stearate
(b)(4)	
Hypromellose	Hypromellose
Titanium dioxide	Titanium dioxide
Macrogol 4000	Macrogol/ (b)(4)
(b)(4)	
Iron oxide red	Red iron oxide (b)(4)
Iron oxide Black	Black Iron oxide (b)(4)
(b)(4)	
(b)(4)	(b)(4)
Iron oxide yellow	
(b)(4)	
(b)(4)	
(b)(4)	

RLD	Test Product
(b)(4)	

Assessment: **Adequate**

Strength	Product Description
24 mg/ 26 mg	Purple colored, oval shaped, biconvex, film coated tablets one side debossed with 'M' and other side debossed with 'S1' (b)(4)
49 mg/51 mg	Light yellow to yellow colored, oval shaped, biconvex, film coated tablets one side debossed with 'M' and other side debossed with 'S2' (b)(4)
97 mg/ 103 mg	Light pink to pink colored, oval shaped, biconvex, film coated tablets one side debossed with 'M' and other side debossed with 'S3' (b)(4)

The firm provided adequate information regarding to components and composition of the drug product.

(b)(4)

There are some minor differences in compositions between the generic proposed formulation and the formulation of the reference product, but they should not have any effects on the quality of the drug products.

However, whether the difference between this proposed formulation and the RLD present any potential concerns with respect to therapeutic equivalence of drug product would rely on the evaluation of Division of Bioequivalence.

The size and shape of generic Sacubitril and Valsartan tablets meets the requirements as per "Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules" as shown in the table below.

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-
-
-
-
-

(b)(4)

Assessment: Adequate

(b)(4)

R REGIONAL INFORMATION

Environmental

Assessment: Adequate

Methods Validation or Verification Package

Assessment: Adequate

Comparability Protocols

Assessment: Choose an item.
N/A

Lifecycle Management Considerations

DRUG PRODUCT LIST OF DEFICIENCIES (from Review 1A)

1.	
2.	
3.	

(b)(4)

DRUG PRODUCT LIST OF DEFICIENCIES (from Review 1)

1.	
2.	
3.	

(b)(4)

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CHAPTER III: ENVIRONMENTAL

R REGIONAL INFORMATION

Environmental

Assessment:

Adequate

CHAPTER IV: LABELING

R REGIONAL INFORMATION

1.14 Labeling

Labeling & Prescribing Information

DESCRIPTION (Rx insert or Active Ingredient(s), and Inactive Ingredients in DRUG FACTS for OTC):

Is the information accurate? ☒ Yes ☐ No

If "No," explain.

Is the drug product subject of a USP monograph? ☐ Yes ☒ No

If "Yes," does labeling have accurate USP statement in the DESCRIPTION (for Rx) or Other Information section of DRUG FACTS (for OTC)?

☐ Yes ☐ No ☐ Statement not needed

If NO, what is/are the needed statement(s)? _____

HOW SUPPLIED section (Rx insert) or Storage (in DRUG FACTS for OTC)

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Is tamper evident feature provided in the container/closure for the OTC products or Controlled Substance (CII – CIV) products? ☐ Yes ☐ No
☒ N/A (NOT OTC or Controlled Substance)

If "No," explain.

For solid oral drug products, only: drug product length(s) of commercial batch(es):

ANDA Strength	Length (MM)	Imprint Code
24 mg/ 26 mg	10.00 x 4.00	one side debossed with 'M' and other side debossed with 'S1'
49 mg/ 51 mg	13.00 x 5.10	one side debossed with 'M' and other side debossed with 'S2''
97 mg/ 103 mg	15.00 x 5.90	one side debossed with 'M' and other side debossed with 'S3''

Send issue to the Labeling assessor through the Platform with a list of quality-related labeling deficiencies and also record reference number or link for all the issues:

Issue Description	Issue Reference Number or Link

LABELING LIST OF DEFICIENCIES

None

ATTACHMENT II: List of All Deficiencies (from Review Cycle #2)

Drug Substance Deficiencies

1.

(b)(4)

Drug product

1.

(b)(4)

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(b)(4)

A. Labeling Deficiencies

None

(END OF DRUG PRODUCT QUALITY ASSESSMENT)

Concur with deficiencies

Signature Block (Review 1):

Primary DP Assessor:	<i>Qiuxia Wang</i>	Date:	<i>10/31/2019, 12/18/19</i>
Secondary DP Assessor:	<i>Raghu Samy</i>	Date:	<i>11/22/19, 12/18/19</i>

Signature Block (Review 1A):

Concur with deficiencies

Primary DP Assessor:	<i>Qiuxia Wang</i>	Date:	<i>3/19/2020, 5/28/2020</i>
Secondary DP Assessor:	<i>Raghu Samy</i>	Date:	<i>4/7/2020, 5/28/2020</i>



DRUG PRODUCT QUALITY ASSESSMENT

ANDA 213748 (Review Cycle # 01)A

Sacubitril and Valsartan

24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg

RECOMMENDATION

☐ Complete Response-Major
☒ Complete Response-Minor
☐ Discipline Review Letter (DRL)
☐ Information Request—IR x Days
☐ Approval

Reviewer's Name

Qiuxia Wang

Division of Immediate Release Products I/Branch II

Office of Lifecycle Drug Products

Office of Pharmaceutical Quality

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ANDA 213748 (Assessment Cycle # 01)A

Drug Product Name	Sacubitril and Valsartan Tablets
USP Monograph	☐ Yes ☒ No
Strength	24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg
Dosage Form	Tablets
Route of Administration	Oral
Rx/OTC Dispensed	☒ Rx ☐ OTC
ANDA Applicant	MSN Laboratories Private Limited
Drug Product Manufacturer	☒ Same as the Applicant ☐ Different from the Applicant (see below)
US agent, if applicable	☐ N/A ☒ (See Below) MSN Pharmaceuticals Inc. 20 Duke Road, Piscataway, NJ 08854-3714
Proposed Indication	Sacubitril and Valsartan Tablets indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure and reduced ejection fraction.

Submission(s) Assessed	Document Date	Discipline(s) Affected
Amendment-Response to DRL	2/27/2020	Quality
Original	7/8/2019	All
Labeling-Response to Discipline Review Letter*	10/30/2019	Labeling

*Preparation of oral suspension added in label to be in line with RLD, but no supporting quality information provided

QUALITY ASSESMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Reviewed	Comments
(b)(4)	II	(b)(4)	Sacubitril and Valsartan	Inadequate	5/13/20	By Donglei Yu
Other DMF: ☐ N/A ☒ (See Below)						
(b)(4)	III	(b)(4)				
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	IV					
	IV					
	IV					
	Other					

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved ANDA*

Document	Application Number	Brand Name	Description
NDA	207620	ENTRESTO®	Sacubitril and Valsartan Tab, 24/26, 49 /51, 97 /103 mg

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH-ODE	N/A			
CDRH-OC	N/A			
Clinical	N/A			
Other	N/A			

PART I. Review of Firm's Response to Deficiencies

*((Note to reviewers: PART I is **not applicable** for review of **original ANDA**. At time of review of an amendment, move your cursor over the heading for "PART I", click the "Paragraph" dialog box in the Quick Access Toolbar, uncheck the checkbox next to "Collapsed by default", and then click the small triangle at the left of "PART I" to expand and display the body text.))*

CHAPTER I: DRUG SUBSTANCE

IQA ANDA Assessment Guide Reference

Drug Substance Name	Sacubitril and Valsartan
DMF Number (If Applicable)	(b)(4)
DMF Status	New DMF - Pending Review
DMF Holder	(b)(4)

Overall Assessment Recommendation for DS: **Inadequate - Major**

Theme:

☐ N/A	☐ Other (Requires Division Director Approval)
☒ DMF	☐ Due to Consult
☐ New DS Batch	

Justification: view justification statements found at: [Justification Statements](#)

Paste appropriate justification statement(s) here or insert "N/A" if not applicable.
Other (Requires Division Director Approval)- Assessor writes justification here if "other" selected as theme.

Justification for Major from DMF review

An unqualified impurity (toxicology studies required to qualify the impurity): New toxicology studies are requested for the unqualified impurity and the review of these studies requires substantial expenditure of FDA resources and will potentially affects other aspects of the application and the related conclusions.

Highlight Key Issues from Last Cycle and Their Resolution:

No Key issues with DS from last cycle review

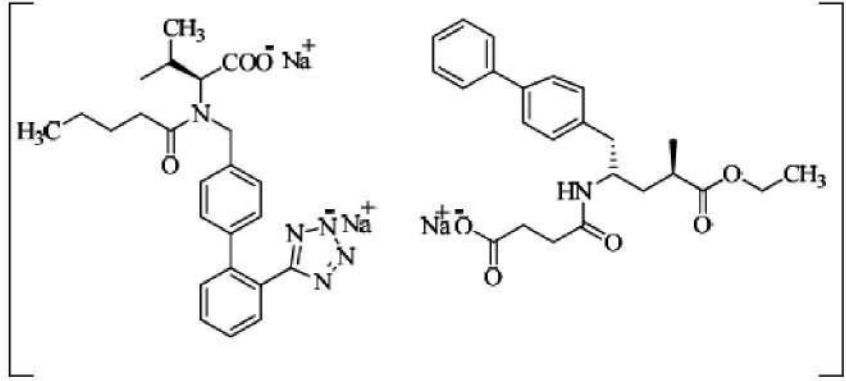
Concise Description of Outstanding Issues:

Below is a brief description of outstanding issues with DS in ANDA:

Inadequate DMF-Major

Select Number of Approved Comparability Protocols: 0

S.1 GENERAL INFORMATION

Recommended International Nonproprietary Name	Sacubitril and Valsartan
USAN	Sacubitril and Valsartan
Chemical Name(s)	Tri sodium (4- { [(1 S,3R)-1-([1,1'-biphenyl] 4-yl)methyl)-4-ethoxy-3-methyl-4-oxobutyl]amino } -4-oxobutanoate)-(N-pentanoyl-N-{[2'-(1H-tetrazol-1-yl-5-yl)[1,1'-biphenyl]-4-yl]methyl }-L-valinate)
CAS Number	936623-90-4
Therapeutic Category	To treat heart failure
Structure	
Molecular Formula	C ₄₈ H ₅₅ N ₆ O ₈ Na ₃
Molecular Weight	912.96

Description White to almost white powder.

(b)(4)

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(b) (4)

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(b)(4)

Assessment:

Adequate

Deficiency in Review 1:

(b)(4)

(b)(4)

(Satisfactorily
addressed in the amendment dated 2/27/2020)

Post-Approval Stability Protocol and Commitment

Assessment:

Adequate

Refer to DMF review

R REGIONAL INFORMATION

Comparability Protocols ☒ *N/A* ☐ *(See Below)*

Assessment:

Choose an item.

Lifecycle Management Considerations

DRUG SUBSTANCE LIST OF DEFICIENCIES (from Review 1A):

(b)(4)

DRUG SUBSTANCE LIST OF DEFICIENCIES (from Review 1):

1.

2.

(b)(4)

Retest period for drug substance.

CHAPTER II: DRUG PRODUCT

[IQA ANDA Assessment Guide Reference](#)

Overall Assessment Recommendation:

Inadequate - Minor

Theme:

☒ N/A	☐ Unacceptable Analytical Methods
☐ Unqualified Impurity	☐ Application Quality
☐ New DP Batch	☐ Pharmaceutical Equivalence
☐ Product Design	☐ Product Safety
☐ Failing Stability Data	☐ Other (Requires Division Director Approval)
☐ Application Completeness	☐ Due to Consult

Justification: view justification statements found at: [Justification Statements](#)

Paste appropriate justification statement(s) here or insert "N/A" if not applicable.
Other (Requires Division Director Approval)- Assessor writes justification here if "other" selected as theme.

Assessment Summary:

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking After Assessment Cycle #	Comments

Note: This table will be updated in Executive Summary at time of approval.

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Concise Description of Outstanding Issues (*List Bullet Points with Key Information and Update as Needed*): see deficiency letter

Select Number of Approved Comparability Protocols: 0

List Current Quality Endorsement Status:

- USP monograph for Drug Product and compliance (current USP) – status: not USP
- Dissolution status: specifications are not finalized with Biopharmaceutics, and implemented, and stability data complies with revised specifications (if applicable) to confirm shelf life proposal

- Elemental impurity compliance with ICH Q3D – status: adequate
- Number of Comparability protocols included: 0

P.1 DESCRIPTION AND COMPOSITION

The quantitative composition and function of each excipient in the drug product is listed.

Ingredients	Functions	24 mg/ 26 mg (mg/tablet)	% w/w	49 mg/ 51 mg (mg/tablet)	% w/w	97 mg/ 103 mg (mg/tablet)	% w/w	Maximum Levels (dosage per unit) (mg)	IIG Limit for Oral Route of Administration (mg)
Intragramular									
Sacubitril and Valsartan	Active ingredient	(b)(4)							
Microcrystalline Cellulose (b)(4) USP-NF	(b)(4)								
Crospovidone (b)(4) USP-NF									
Croscarmellose Sodium (b)(4) USP-NF									
Colloidal Silicon Dioxide (b)(4) USP-NF									
Talc (b)(4) USP									
Magnesium Stearate (b)(4) USP-NF									
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Ingredients	Functions	24 mg/ 26 mg (mg/tablet)	% w/w	49 mg/ 51 mg (mg/tablet)	% w/w	97 mg/ 103 mg (mg/tablet)	% w/w	Maximum Levels (dosage per unit) (mg)	IIG Limit for Oral Route of Administration (mg)
(b)(4)									
Coated Tablet weight		103.000	100.00	206.000	100.00	412.000	100.00	-	-

(b)(4)

RLD	Test Product
Microcrystalline Cellulose	Microcrystalline Cellulose (b)(4)
Crospovidone	Crospovidone -
Low-substituted hydroxypropyl Cellulose	Croscarmellose sodium
Colloidal silicon dioxide	Colloidal silicon dioxide
Talc	Talc (b)(4)
Magnesium stearate	Magnesium stearate
(b)(4)	
Hypromellose	Hypromellose
Titanium dioxide	Titanium dioxide
Macrogol 4000	Macrogol/ (b)(4)
(b)(4)	
Iron oxide red	Red iron oxide (b)(4)
Iron oxide Black	Black Iron oxide (b)(4)
(b)(4)	
(b)(4)	(b)(4)
Iron oxide yellow	(b)(4)
(b)(4)	(b)(4)
(b)(4)	

RLD	Test Product
(b)(4)	

Assessment:

Adequate

Strength	Product Description
24 mg/ 26 mg	Purple colored, oval shaped, biconvex, film coated tablets one side debossed with 'M' and other side debossed with 'S1' and (b)(4)
49 mg/51 mg	Light yellow to yellow colored, oval shaped, biconvex, film coated tablets one side debossed with 'M' and other side debossed with 'S2' (b)(4)
97 mg/ 103 mg	Light pink to pink colored, oval shaped, biconvex, film coated tablets one side debossed with 'M' and other side debossed with 'S3' (b)(4)

The firm provided adequate information regarding to components and composition of the drug product.

(b)(4)

There are some minor differences in compositions between the generic proposed formulation and the formulation of the reference product, but they should not have any effects on the quality of the drug products.

However, whether the difference between this proposed formulation and the RLD present any potential concerns with respect to therapeutic equivalence of drug product would rely on the evaluation of Division of Bioequivalence.

The size and shape of generic Sacubitril and Valsartan tablets meets the requirements as per "Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules" as shown in the table below.

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-
-
-

(b)(4)

Assessment: Adequate

(b)(4)

R REGIONAL INFORMATION

Environmental

Assessment: Adequate

Methods Validation or Verification Package

Assessment: Adequate

Comparability Protocols

Assessment: Choose an item.
N/A

Lifecycle Management Considerations

DRUG PRODUCT LIST OF DEFICIENCIES (from Review 1A)

1.	
2.	
3.	

(b)(4)

DRUG PRODUCT LIST OF DEFICIENCIES (from Review 1)

1.	
2.	
3.	

(b)(4)

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CHAPTER III: ENVIRONMENTAL

R REGIONAL INFORMATION

Environmental

Assessment:

Adequate

CHAPTER IV: LABELING

R REGIONAL INFORMATION

1.14 Labeling

Labeling & Prescribing Information

DESCRIPTION (Rx insert or Active Ingredient(s), and Inactive Ingredients in DRUG FACTS for OTC):

Is the information accurate? ☒ Yes ☐ No

If "No," explain.

Is the drug product subject of a USP monograph? ☐ Yes ☒ No

If "Yes," does labeling have accurate USP statement in the DESCRIPTION (for Rx) or Other Information section of DRUG FACTS (for OTC)?

☐ Yes ☐ No ☐ Statement not needed

If NO, what is/are the needed statement(s)? _____

HOW SUPPLIED section (Rx insert) or Storage (in DRUG FACTS for OTC)

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Is tamper evident feature provided in the container/closure for the OTC products or Controlled Substance (CII – CIV) products? ☐ Yes ☐ No
☒ N/A (NOT OTC or Controlled Substance)

If "No," explain.

For solid oral drug products, only: drug product length(s) of commercial batch(es):

ANDA Strength	Length (MM)	Imprint Code
24 mg/ 26 mg	10.00 x 4.00	one side debossed with 'M' and other side debossed with 'S1'
49 mg/ 51 mg	13.00 x 5.10	one side debossed with 'M' and other side debossed with 'S2''
97 mg/ 103 mg	15.00 x 5.90	one side debossed with 'M' and other side debossed with 'S3''

Send issue to the Labeling assessor through the Platform with a list of quality-related labeling deficiencies and also record reference number or link for all the issues:

Issue Description	Issue Reference Number or Link

LABELING LIST OF DEFICIENCIES

None

ATTACHMENT II: List of All Deficiencies (from Review 1A)

Drug Substance Deficiencies

1.

(b)(4)

Drug product

1.

2.

(b)(4)

3.

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4.

5.

(b)(4)

6.

7.

A. Labeling Deficiencies

None

(END OF DRUG PRODUCT QUALITY ASSESSMENT)

Concur with deficiencies

Signature Block (Review 1):

Primary DP Assessor:	<u>Qiuxia Wang</u>	Date:	<u>10/31/2019,</u> <u>12/18/19</u>
Secondary DP Assessor:	<u>Raghu Samy</u>	Date:	<u>11/22/19,</u> <u>12/18/19</u>

Signature Block (Review 1A):

Concur with deficiencies

Primary DP Assessor:	<u>Qiuxia Wang</u>	Date:	<u>3/19/2020,</u> <u>5/28/2020</u>
Secondary DP Assessor:	<u>Raghu Samy</u>	Date:	<u>4/7/2020,</u> <u>5/28/2020</u>



Qiuxia
Wang

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Date: 5/28/2020 09:49:01AM
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Raghu
Samy

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MEMORANDUM

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

DATE: February 21, 2020

TO: Bing Li, Ph.D.
Director (Acting)
Office of Bioequivalence
Office of Generic Drugs

FROM: Srinivas R. Chennamaneni, Ph.D.
Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Charles R. Bonapace, Pharm.D.
Director
DNDSI, OSIS

SUBJECT: Routine inspection of Cliantha Research Ltd., Sigma-1
Corporate, Bodakdev, Ahmedabad, Gujarat, India.

1 Inspection Summary

(b)(4)

1.1. Recommendation

After reviewing the inspectional findings, I conclude that the clinical data from the audited studies are reliable.

2 Inspected Studies:

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(b)(4)

Srinivas Rao

Chennamaneni -S

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ou=People,
0.9.2342.19200300.100.1.1=2001584247,
cn=Srinivas Rao Chennamaneni -S
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Srinivas R. Chennamaneni, Ph.D.

Gopa Biswas -S

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Gopa Biswas, Ph.D.

Charles R.

Bonapace -S

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ou=People,
0.9.2342.19200300.100.1.1=1300156609,
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Date: 2020.02.24 22:08:42 -05'00'

Charles R. Bonapace, Pharm.D.

Attachment-1

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M E M O R A N D U M

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

DATE: December 20, 2019

TO: Bing Li, Ph.D.
Director (Acting)
Office of Bioequivalence
Office of Generic Drugs

FROM: Srinivas R. Chennamaneni, Ph.D.
Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Charles R. Bonapace, Pharm.D.
Director
DNDSI, OSIS

SUBJECT: Routine inspection of Cliantha Research Ltd., Sigma-1
Corporate, Bodakdev, Ahmedabad, Gujarat, India.

1 Inspection Summary

(b)(4)

1.1. Recommendation

After reviewing the inspectional findings, I conclude that the clinical data from the audited studies are reliable.

2 Inspected Studies:

(b)(4)

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(b)(4)

Srinivas Rao

Chennamaneni -S

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ou=People,
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Date: 2019.12.20 13:24:05 -05'00'

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Mohsen Rajabi-
abhari -S

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Mohsen Rajabi Abhari, Ph.D.

Charles R.
Bonapace -S

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

DATE: 8/19/2019

TO: Office of Bioequivalence
Office of Generic Drugs

FROM: Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: ANDA
ANDA
ANDA
ANDA
ANDA (b)(4)
ANDA
ANDA
ANDA
ANDA
ANDA 213748
ANDA
ANDA
ANDA (b)(4)
ANDA

The Division of Generic Drug Bioequivalence Evaluation (DGDBE) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the site listed below. The rationale for this decision is noted below.

Rationale

OSIS inspected the site in August 2018, which falls within the surveillance interval. The inspection was conducted under the following submissions: ANDAs (b)(4)

The final classification for the inspection was No Action Indicated (NAI).

Therefore, based on the rationale described above, an inspection is not warranted at this time.

Inspection Site

Facility Type	Facility Name	Facility Address
Analytical	(b)(4)	

Timely Consults and Early IR Checklist for Type II API DMFs

Result: TCIR-NAI

ANDA#: 213748

Drug Product: SACUBITRIL AND VALSARTAN, tablet, 49mg || 51mg || 97mg || 103mg
|| 24mg || 26mg

DMF#:

DMF Subject (API name): SACUBITRIL AND VALSARTAN (FORM-S)

Note: If the DMF is for a mixture of the API and excipient(s) (e.g. stabilizer, buffer), email DMF OGD Mailbox (DMFOGD@fda.hhs.gov) and include the URL to the project; example "this TCIR is for an API excipient mixture".). Note to reviewer: Do not archive the TCIR document as changes may need to be made.

Notes: This DMF is for a mixture of the two APIs (SACUBITRIL AND VALSARTAN (FORM-S)). The firm performs a salt conversion on valsartan to the disodium salt and processes into the mixture with sacubitril in n-heptane. No synthesis of either individual API is included in this DMF. Since each API is isolated prior to forming the mixture establishing "sameness" should not be an issue.

This DMF refers to the following DMFs for the individual APIs.

Valsartan:

Sacubitril:

1. Are there any intermediate facilities **listed in the 356h**? ☐ Yes ☒ No

If yes, determine if the intermediate facility is critical.

Facility Name and Address	FEI/DUNS	Intermediate critical (Y/N)	Justification*
* If an intermediate facility is identified, please select justification(s) from the following: 1. The intermediate is not separated by an adequate number of steps from the final API. The risk to DS quality cannot be adequately mitigated through the intermediate specification and thereby the facility warrants evaluation.			

2. The intermediate route of synthesis involves unusual or complex chemistry which presents a risk to DS quality that cannot be adequately mitigated through the intermediate specification.
3. The drug substance is very complex, and the intermediate route of synthesis introduces the most critical structural features and the risk to DS quality cannot be adequately mitigated through the intermediate specification.
4. Intermediate is not deemed critical because the criteria above do not apply.
5. The intermediate would be deemed critical if new, but the current intermediate facility was a pre- existing facility and was not evaluated for other applications.

2. Does the Type II API DMF list any manufacturing facilities, critical intermediate facilities, or testing facilities for routine release or stability testing that are **not listed in the facility profile and/or on the 356h** form for the referencing ANDA? ☐Yes ☒No

If yes, include the information identifying each facility and its function below:

Facility Name and Address [#]	Function ^{\$}	Justification if Intermediate facility*	FEI/DUNS [#]

* If an intermediate facility is identified, please select justification(s) from the following:

1. The intermediate is not separated by an adequate number of steps from the final API. The risk to DS quality cannot be adequately mitigated through the intermediate specification and thereby the facility warrants evaluation.
2. The intermediate route of synthesis involves unusual or complex chemistry which presents a risk to DS quality that cannot be adequately mitigated through the intermediate specification.
3. The drug substance is very complex, and the intermediate route of synthesis introduces the most critical structural features and the risk to DS quality cannot be adequately mitigated through the intermediate specification.
4. Intermediate is not deemed critical because the criteria above do not apply.
5. The intermediate would be deemed critical if new, but the current intermediate facility was a pre- existing facility and was not evaluated for other applications.

§ CSN: Non-Sterile API by Chemical Synthesis

CSS: Sterile API by Chemical Synthesis

CSP: Chemical Sterilization

CTL: Control Testing Laboratories

CTB: Control Testing Laboratories "Also"

CTX: Control Testing Laboratories "Also" (Drugs)

CXA: Plant/Animal Extraction Purified API

CFN: Non –Sterile API by Fermentation

CFS: Sterile API by Fermentation

CRU: API Non-Sterile/Intermediate

Note: Add "-Critical Intermediate" to the appropriate manufacturing code if the site manufactures a critical intermediate.

#Note: *Not for FOI boxes (refer to SOP for format) need to be used if the facility information is submitted in a secondary DMF.*

RBPM to include the following comment in the early-IR sent to the applicant:

n/a

RBPM to include the following modified comment in the early-IR sent to the applicant if the facility information is submitted in a secondary DMF:

"Please note that there is a manufacturing facility (critical intermediate) that is included in a DMF referenced by [Primary DMF#] for [API name] that was not included on your form 356h. Please contact your DMF holder to resolve any discrepancies and clarify which DMF related facilities support your application. Please note that a revised 356h form will be required to add any new facilities to your application. The addition of a new facility or new facilities may result in an extension of the performance goal date for your submission."

3. Does the DMF include any data (e.g. Ames study or cited literature studies) that requires a pharm/tox consult?

☐ Yes ☒ No

If yes, prepare the consult and send to DCR in Panorama and enter date sent below.

Consult form date:

4. After examining the labelling for the drug product:

Is a DCR consult required to establish the Maximum Daily Dose (MDD)? ☐Yes ☒No

Is a DCR consult required to establish the product use (i.e. duration and frequency of use, patient population)? ☐Yes ☒No

The following question applies to drug products indicated for the treatment of cancer.

Is a consult required to determine if the drug product is indicated for the treatment of advanced cancer in the context of ICH S9? ☐Yes ☐No

Is a DCR consult required to determine that the drug substance is carcinogenic? ☐Yes
☐No

If yes to any of the above prepare the appropriate consult and send to DCR in Panorama and enter date sent below.

Consult form date:



David
Skanchy

Digitally signed by David Skanchy
Date: 7/12/2019 11:57:57AM
GUID: 508da7020002879dab02d51b50cc9c3d

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 213748

BIOEQUIVALENCE REVIEW(s)

BIOPHARMACEUTICS ASSESSMENT	
Application No.	ANDA-213748-ORIG-1-AMEND-8
Submission Type	Solicited Major Amendment
Applicant	MSN LABORATORIES PRIVATE LIMITED
Product Name	Sacubitril and Valsartan Tablets
Dosage Form/Strengths	IR Tablet; 24 mg/26 mg, 49 mg/51 mg and 97mg/103 mg
Route of Administration	Oral
Indication	• 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.
Submission Date	8/19/20
Goal Date	4/18/2021
Primary Reviewer	Ho-Pi Lin, Ph.D.
Secondary Reviewer	N/A
Recommendation	ADEQUATE

EXECUTIVE SUMMARY

Background:

This amendment (#8) was submitted in response to the complete response (CR) letter issued on 6/8/2020 for the original submission. Previous assessment was documented in Panorama.¹ The assessment concluded inadequate was due to inadequate dissolution acceptance criterion.

Previous CR Comments

Based on the provided information and data, the proposed dissolution method [USP 1 (basket) at 75 rpm/900 mL of pH 6.8 phosphate buffer] is deemed adequate for quality control testing of the proposed drug product. However, the provided dissolution data support a dissolution acceptance criterion and therefore the proposed acceptance criterion is not acceptable. Implement the following dissolution acceptance criterion for all strengths of your proposed product, Sacubitril and Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg and 97/103 mg:
“NLT % (Q) in 20 minutes” [for both sacubitril and valsartan]

¹

<https://panorama.fda.gov/internal/document/preview?versionID=5eac76cf01b56ba5c2cd6ace37d442ec&ID=5dfd0f2d0014e7e092033c3228682dac>

Update your drug product release and stability specifications accordingly. In addition, please be advised, that all proposed exhibit batches are expected to meet these revised dissolution specifications in your stability program through your proposed expiry period. If dissolution failures are observed on stability, these should be described. Discuss any corrective actions to avert such dissolution failures and provide data from a new batch to demonstrate correction of the issue, if needed.

Biopharmaceutics Assessment:

The Applicant accepted² and implemented³ the recommended criterion. The response is acceptable.

Recommendation:

This ANDA 213748 is recommended for approval from a biopharmaceutics perspective.

Approved disintegration method and acceptance criterion/criteria:

USP Apparatus	Speed	Medium/Temperature	Acceptance criterion(a)
I (Basket)	75 rpm	pH 6.8 phosphate buffer/37°C 900 ml	Q= % in 20 minutes (Sacubitril & Valsartan)

² Page 5 in <file:///C:/cdsesub1/evsprod/ANDA213748/0007/m1/us/1-2-cover-letters/response-to-crl-0007.pdf>

³ <file:///C:/cdsesub1/evsprod/ANDA213748/0007/m3/32-body-data/32p-drug-prod/sac-vlsrtn-tab-msn-lab/32p5-contr-drug-prod/32p51-spec/specifications.pdf>



Ho-Pi
Lin



Digitally signed by Ho-Pi Lin

Date: 3/10/2021 09:02:51AM

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BIOPHARMACEUTICS ANDA REVIEW	
Application No.	ANDA 213748-ORIG-1
Applicant	MSN Laboratories Private Ltd.
Product Name/Strength	Sacubitril/Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg
Dosage Form/ Route of Administration:	Tablets/Oral
Indication	(b)(4)
Submission Date(s)	07/07/2019 – Original Submission 02/ 27/2020 – IR Response
RLD/RS	ENTRESTO® Tablets, 24mg/26mg,49mg/51mg & 97mg/103mg (NDA# 207620)
Primary Reviewer	Mathew John, Ph.D.
Secondary Reviewer	Om Anand, Ph.D.
Recommendation	Inadequate-Minor

Executive Summary: This Biopharmaceutics Review evaluates data supporting the adequacy of the proposed dissolution method and acceptance criteria for the proposed drug product.

The proposed drug product, Sacubitril/Valsartan Tablets, (b)(4)

(b)(4)

The Applicant originally proposed to use (b)(4)

(b)(4)

(b)(4)

The FDA's dissolution database was updated on October 24, 2019 to propose testing Sacubitril/Valsartan Tablets using USP Apparatus I (Basket) (b)(4)

(b)(4) In the Original submission, the Applicant did not provide adequate data demonstrating the suitability of the originally proposed dissolution method (b)(4)

Considering the (b)(4) solubility of Sacubitril/Valsartan and due to (b)(4) data for some of the batches, the Applicant was asked to explain and justify the (b)(4)

(b)(4) and demonstrate the suitability of the originally proposed dissolution method. The Applicant was also recommended that if using the originally proposed dissolution method (b)(4)

(b)(4) the dissolution of the proposed drug product remains (b)(4) is noticed; then the Applicant may consider the new FDA's dissolution database method for the quality control testing of their proposed drug product.

In a response (dated 02/27/2020,) to IRs, the Applicant revised the dissolution method, and adopted² the current FDA's dissolution database method for the quality control (QC) testing of the

¹ FDA Recommended Dissolution Methods

² \\cdsesub1\evsprod\anda213748\0005\m2\27-clin-sum\pivotal-cdp-report.pdf

drug product. The updated dissolution method and acceptance criterion submitted by the Applicant are tabulated in Table 1 below.

Table 1: Updated dissolution method and acceptance criterion proposed by the Applicant

Method Source	USP Apparatus	Speed (RPMs)	Medium	Volume/Temp (mL/°C)	Proposed Acceptance Criterion
(b)(4)					

The newly proposed dissolution method is acceptable. However, the proposed acceptance criterion is (b)(4) and not acceptable, therefore an IR will be sent to revise the dissolution acceptance criteria to NLT (b)(4) % (Q) in 20 minutes” [for both sacubitril and valsartan] for all strengths of the drug product.

Biopharmaceutics Recommendation: The Biopharmaceutics recommendation for ANDA 213748 for the proposed Sacubitril/Valsartan Tablets, is **pending** due to the outstanding response to the Information Request (IR) comment regarding the dissolution acceptance criterion.

Reviewer's Assessment

1. **Solubility:** The Applicant's provided solubility data indicate (b)(4)

(b)(4)

2. **Formulation:** The proposed formulation is (b)(4)

(b)(4)

3. **Bioequivalence and PK Characteristics of the drugs:** T_{max} for sacubitril, LBQ657 (active metabolite of sacubitril), and valsartan are 0.5 hours, 2 hours, and 1.5 hours, respectively. The oral absolute bioavailability of sacubitril is estimated to be $\geq 60\%$. [Ref. Labeling]. The Applicant performed in-vivo bioequivalence studies using the proposed test and the RS products. The Applicant submitted bioequivalence study results were evaluated by the Division of Bioequivalence / OGD and was deemed inadequate⁵.

4. **Dissolution Method:** In the original submission, the Applicant used (b)(4)

(b)(4) In the original submission, the Applicant provided limited data/information demonstrating the suitability of the proposed dissolution method for the proposed drug product. Using the proposed dissolution method, the biobatch exhibited at

(b)(4)

In the response to the IRs⁶, the Applicant accepted FDA's recommendation and adopted⁷ the current FDA's dissolution database method for QC dissolution studies of the drug product. The updated dissolution method submitted by the Applicant is tabulated in Table 1. The Applicant demonstrated the limited discriminating ability of the new dissolution method in terms of

³ \\cdsesub1\evsprod\ANDA213748\0000\m3\32-body-data\32s-drug-sub\sacu-vals-msn-life-sciences-pvt-ltd\32s1-gen-info

⁴ \\cdsesub1\evsprod\anda213748\0000\m2\23-qos\qos-ds-word.doc

⁵ <https://panorama.fda.gov/document/preview?versionID=5df7d772007be5324bcd0016b3019064&ID=5de99fbb002c8bc85574b04e53bbcd21>

⁶ \\cdsesub1\evsprod\anda213748\0005\m1\us\1-2-cover-letters\response-to-drl-0005.pdf

⁷ \\cdsesub1\evsprod\anda213748\0005\m2\27-clin-sum\pivotal-cdp-report.pdf

critical formulation variables and hardness of the Tablet. Therefore, based on the totality of the data and justifications provided by the Applicant, the newly proposed dissolution method (Basket/75 rpm) is acceptable.

5. **Dissolution Acceptance Criterion:** Using the new dissolution method, the dissolution data of all batches of both sacubitril and valsartan in 24 mg/26 mg and 49 mg/51 mg Tablet strengths show (b)(4) % in (b)(4). The dissolution data for all batches of 97/103 mg Tablet strength exhibit a minimum release of (b)(4) % in 20 minutes⁸. The Applicant proposed acceptance criterion is (b)(4); and therefore an IR will be sent to tighten the dissolution acceptance criteria as NLT (b)(4) % (Q) in 20 minutes” [for both sacubitril and valsartan] for all strengths of the drug product.
6. **Dissolution Risk/Mitigation Assessment:** Biopharmaceutics/dissolution risk is relatively high because (b)(4). The dissolution method and acceptance criterion are set appropriately to mitigate the risk of the change in the drug product performance.

Additional Note: The originally posted dissolution method (b)(4)

(b)(4)

(b)(4) the Applicant proposed dissolution method using USP Type-I basket method at rotational speed of 75 rpm. This new method was found to be acceptable for the NDA and therefore, i) due to the limitations of the original method; and ii) due to the change in the dissolution method followed by the NDA; the FDA dissolution database was updated with the new dissolution method [900 mL of Phosphate Buffer, pH 6.8 using USP apparatus 1 (basket) at 75 rpm].

⁸ [\\cdsesub1\evsprod\anda213748\0005\m2\27-clin-sum\pivotal-cdp-report.pdf](#)

LIST OF COMMENTS FOR THE INFORMATION REQUEST # 2

Based on the provided information and data, the proposed dissolution method [USP 1 (basket) at 75 rpm/900 mL of pH 6.8 phosphate buffer] is deemed adequate for quality control testing of the proposed drug product. However, the provided dissolution data support a dissolution acceptance criterion and therefore the proposed acceptance criterion is not acceptable. Implement the following dissolution acceptance criterion for all strengths of your proposed product, Sacubitril and Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg and 97/103 mg:

“NLT % (Q) in 20 minutes” [for both sacubitril and valsartan]

Update your drug product release and stability specifications accordingly. In addition, please be advised, that all proposed exhibit batches are expected to meet these revised dissolution specifications in your stability program through your proposed expiry period. If dissolution failures are observed on stability, these should be described. Discuss any corrective actions to avert such dissolution failures and provide data from a new batch to demonstrate correction of the issue, if needed.

APPENDIX I

Information Request [dated 12/23/2019] and Response [dated 02/27/2020]

1. The proposed dissolution method [REDACTED] is not acceptable at this stage because [REDACTED]

[REDACTED]

The limited data/information provided are not adequate to demonstrate the suitability/discriminating ability of the proposed dissolution method for your proposed drug product. Please note that the discriminating ability of the dissolution method should be investigated towards the critical material attributes (CMAs), critical process parameters (CPPs) and critical formulation variables (CFVs). In your response, justify the selection of the selected attributes /variables and their levels for demonstrating the discriminating ability of the proposed dissolution method. Described below are our recommendations with respect to proper investigation for the discriminating ability of the proposed dissolution method:

- i. Provide a list of CMAs, CPPs and CFVs affecting the dissolution and establish that your method is discriminating towards those CMAs (including the drug substance particle size distribution), CPPs and CFVs which affect dissolution. In general, the testing conducted to demonstrate the discriminating ability of the dissolution method should compare the dissolution profiles of the proposed drug product(target) and the formulations/product that are intentionally manufactured with meaningful variations, i.e., aberrant formulations and manufacturing conditions with $\pm 10\text{-}20\%$ change to the specification-ranges of these variables for the most relevant CMA's and CPPs.
- ii. In addition, if available, data can be submitted showing that the selected dissolution method is able to reject batches that are not bioequivalent. Supportive dissolution data may also be submitted showing that the selected dissolution method can detect the change(s) in the drug product occurring during the accelerated and stressed conditions.
- iii. Provide i) the manufacturing date, storage conditions and the age of the batches used in the above studies, ii) the number of dosage units used to generate the dissolution data, iii) complete dissolution data (individual, mean, cv%) in tabulated format, and iv) graphic presentation for the mean dissolution data for each table.

The adequacy of the proposed dissolution acceptance criterion will be determined after the accessing the above requested information.

The limited in dissolution data demonstrate that the dissolution of some units of the test product [REDACTED]

[REDACTED] Explain the root cause [REDACTED] of the proposed drug product using your proposed method. Support your explanation with appropriate data. Submit dissolution

(b)(4) profile data using the currently available long-term stability batches. Indicate the age of the batch at the time of dissolution testing.

2. Note that the FDA dissolution database[https://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_SearchResults.cfm] has been updated with a new dissolution method [900 mL of Phosphate Buffer, pH 6.8 using USP apparatus 1 (basket) at 75 rpm]. Please submit dissolution data [(N=12, individual, mean, cv%)] for all your exhibits batches using this method. If using the originally proposed dissolution method (b)(4), the dissolution of your proposed drug product remains incomplete or (b)(4), then you may consider this new FDA method for the quality control testing of your proposed drug product. If you choose to do so, the please submit the information/data showing the suitability/discriminating ability of the proposed dissolution method for your proposed drug product, as per above recommendations regarding the demonstration of the suitability/discriminating ability.

Applicant's Response [dated 02/27/2020]:

The Applicant's detailed response is available at the following link⁹:

The Applicant adopted the dissolution method currently available in the FDA dissolution data base for this drug product as tabulated in Table 1. The Applicant has also submitted the comparative dissolution profiles in section 2.7 of the submission as per the current dissolution method. The Applicant has also studied the discriminative ability of the method in terms of (b)(4)

(b)(4)

Reviewer's Assessment of the response: The Applicant proposed new dissolution method for the proposed drug product is acceptable. However, the proposed dissolution acceptance criterion of Q (b)(4) for all strengths of both Sacubitril and Valsartan is (b)(4) and therefore, the Applicant will be recommended to implement a (b)(4) dissolution acceptance criterion (Please see IR # 2).

⁹ \\cdsesub1\evsprod\anda213748\0005\m1\us\1-2-cover-letters\response-to-drl-0005.pdf

APPENDIX II

Dissolution Profile Data

Figure 1:

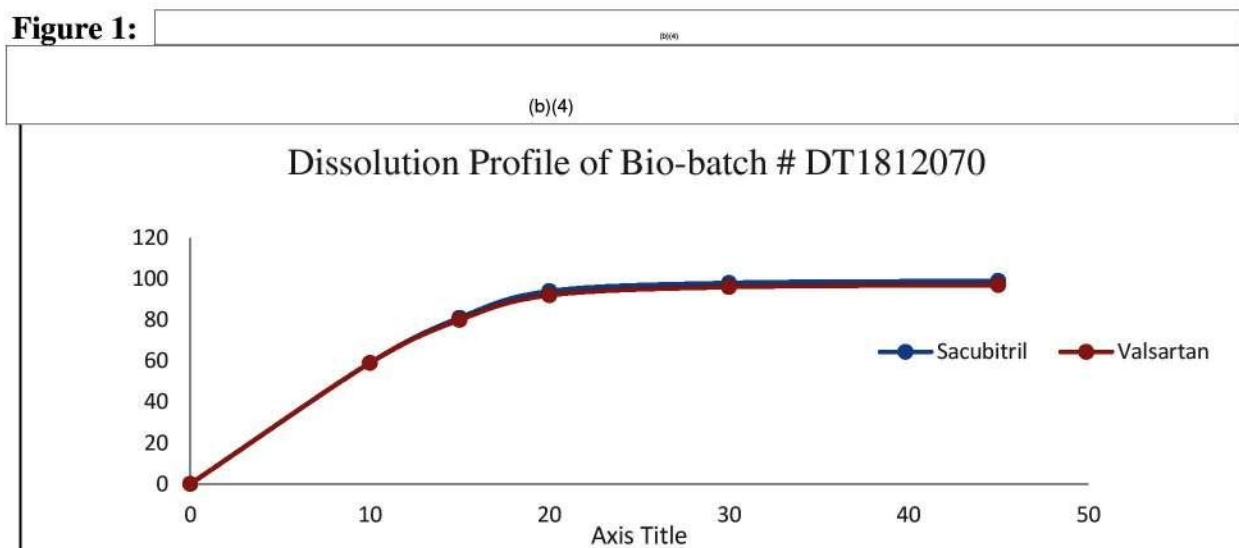
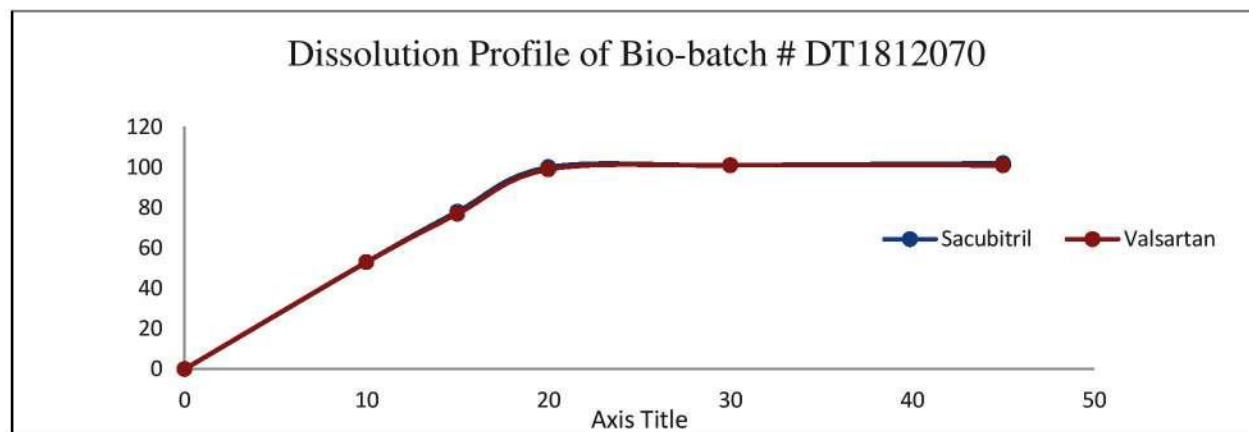


Figure 2: In vitro dissolution profile of drug product strength 97 mg / 103 mg biobatch # DT1812070 using the current method in the FDA dissolution database (USP Apparatus 1/ 75 rpm)¹¹



¹⁰ <\\cdsesub1\evsprod\anda213748\0000\m2\27-clin-sum\pivotal-biosummary-tables-pdf.pdf>

¹¹ <\\cdsesub1\evsprod\anda213748\0005\m2\27-clin-sum\pivotal-cdp-report.pdf>



Using the newly proposed dissolution method, the biobatch and all the exhibit batches shows % drug release by 20 minutes. The submitted dissolution data supports a dissolution acceptance criterion (refer IR #2) and will be communicated to the Applicant.



Om
Anand

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Mathew
John

Digitally signed by Mathew John
Date: 4/23/2020 09:59:31AM
GUID: 5474a078001750e6b83c138c4ba05385

DIVISION OF BIOEQUIVALENCE ASSESSMENT

ANDA No.	213748			
Drug Product Name	Sacubitril; Valsartan Tablets*			
Strength(s)	24 mg; 26 mg, 49 mg; 51 mg, and 97 mg; 103 mg*			
Applicant Name	MSN Laboratories Private Limited			
Applicant Address	MSN House, Plot No. C-24, Industrial Estate, Sanath Nagar, Hyderabad 500018, Telangana, India			
US Contact Name and US Mailing Address	Dr. Kondal Reddy Bairy MSN Pharmaceuticals Inc. 20 Duke Road, Piscataway, NJ 08854-3714			
US Contact Telephone Number	848-200-1906			
US Contact Fax Number	732-902-2113, 501-421-8200			
Original Submission and Amendment(s) Date(s)	07/08/2019 (SD1, Original ANDA Submission) 12/26/2019 (SD5, Response to Bioequivalence Discipline Review Letter [DRL]) 02/27/2020 (SD6, Response to Quality DRL)			
Submission Date(s) of Amendment(s) Under Assessment	N/A [#]			
Primary Assessor	Archana Manerikar, Pharm.D., M.S.			
Secondary Assessor	Amanda Jones, Ph.D.			
Tertiary Assessor	N/A			
Study Number(s)	BA18647467	BA18647468	BA18647469	BA18647470
Study Type(s)	Pilot Fasting	Pilot Fed	Fasting	Fed
Strength(s)	97 mg (Sacubitril); 103 mg (Valsartan)			
Clinical Site	Clantha Research Limited			
Clinical Site Address	Sigma-1 Corporate, B/H Rajpath Club, Opposite Mann Party Plot, Off. S.G. Highway, Bodakdev, Ahmedabad-380 054, Gujarat, India			
Analytical Site	(b)(4)			
Analytical Site Address				
Office of Study Integrity and Surveillance (OSIS) status	<u>Backlog, Year 1 and Year 2 ANDAs</u> ☐ Pending ☐ Complete		<u>Post October 1, 2014 ANDAs</u> ☐ To Be Determined by OSIS ☐ Pending For Cause Inspection ☒ Complete	

	☐ N/A (Waiver/Deem Bioequivalent) ¹	☐ N/A (Waiver/Deem Bioequivalent) ¹
Waiver/Deem Bioequivalent	☒ Granted ☐ Tentatively granted ☐ Not granted ☐ N/A	
QC Dissolution	☐ Pending ☒ Adequate ☐ Inadequate ☐ N/A	
Formulation	☒ Adequate ☐ Inadequate	
Will Response to CR Result in a Reformulation?	☐ Possibly ☐ No ☒ N/A	
Deficiency Classification	☐ Major ☐ Minor/IR ☒ N/A (Review is Adequate)	
Major Deficiency Theme	N/A	
Justification for Major Designation	N/A	
Overall Review Result	☒ Adequate ☐ Inadequate	
Product Specific Guidance (PSG) Referenced in Review	☒ Recommended/Latest Revision Date: <u>Apr 2016</u> RLD Number: <u>NDA 207620</u> ☐ N/A (no PSG available at time of review)	
Revised/New Draft Guidance Generated as Part of Current Review	☐ YES ☒ NO	
Bioequivalence study tracking/supporting document #	Study/test type	Strength
1,5	Fasting	97 mg/103 mg
1,5	Fed	97 mg/103 mg
1,5,6	Waiver/Deem Bioequivalent	24 mg/26 mg, and 49 mg/51 mg
		☒ Adequate ☐ Inadequate

* Please note that throughout this assessment, this drug product may be interchangeably referred to as Sacubitril/Valsartan (SAC/VAL) Tablets, 24 mg/26 mg or 50 mg, 49 mg/51 mg or 100 mg, and 97 mg/103 mg or 200 mg.

The current assignment was made under the 2/9/2022 submission.

1 EXECUTIVE SUMMARY

This is an addendum to the Division of Bioequivalence I (DBI)'s assessment of ANDA 213748 completed on 4/15/2020². The overall assessment outcome was considered ADEQUATE.

¹ Requests submitted under 21 CFR 320.22(d)(2) or 320.24(b)(6).

² GDRP, BE assessment of the discipline review letter response, <https://panorama.fda.gov/internal/document/preview?versionID=5e975ede0018a817ef6ddc55913a4f30&ID=5e8cf6f2000f5cf26f6a8a5554fa3d46>.

This addendum is to document the formulation evaluation of the oral suspension, prepared from 49 mg/51 mg strength of the tablet using Ora-Plus® and Ora-Sweet® SF per reference listed drug (RLD) labeling which includes details on how to prepare the suspension from 49 mg/51 mg strength of the tablet using Ora-Plus® and Ora-Sweet® SF. The RLD labeling also states, “ENTRESTO oral suspension can be substituted at the recommended tablet dosage in patients unable to swallow tablets.” Considering that this drug product is indicated for pediatric as well as renal impaired patients, the test product formulation as suspension was further evaluated. Based on this evaluation, there is no safety concern arising from the suspension of the test product (please refer to section 4 for details). Furthermore, at this time, no additional data will be requested from the applicant to demonstrate bioequivalence (BE) of suspension of the test and reference products (please refer to section 3 for details). The above is consistent with the discussion within Division of Bioequivalence I (DBI) regarding this drug product, where it was decided that the test formulation evaluation of suspension prepared using Ora-Plus® and Ora-Sweet® SF should be conducted for ANDAs for this drug product.

Based on the evaluation (please see Section 2 for details), the suspension formulation of the test product is acceptable.

The test formulation remains adequate from BE perspective. The decision to grant the waiver request for in vivo BE study requirements for the biowaiver strengths, i.e., 24 mg/26 mg and 49 mg/51 mg strengths based on criteria set forth in 21 CFR § 320.22 (d)(2) remains unchanged. The Biopharmaceutics quality assessment which was indicated as pending in the previous BE assessments, is adequate per GDRP as of 4/19/2021³.

The application remains **adequate**.

NOTE TO REGULATORY PROJECT MANAGER: The bioequivalence assessment outcome does not change. No letter will be communicated to the applicant as result of this addendum.

There are three Policy Alerts related to this drug product: Citizen Petition (CP) # FDA-2019-P-1893 and FDA-2021-P-1286, for ENTRESTO® (sacubitril/valsartan) Tablets and CP FDA-2019-P-2869 for multiple valsartan products or drug products containing valsartan.

No Approval Actions (AP/TA) can be taken prior to contacting Policy Lead. All disciplines can continue communications (CRL, IR/DRL).

³ GDRP, Biopharmaceutics review,
<https://panorama.fda.gov/internal/document/preview?versionID=607dc0ed011a7b2b7717ae97a9ee9a74&ID=6048d0c60062c40221b02ada122c156d>.

2 APPENDIX

2.1 Test Formulation⁴

Ingredient	Amount (mg) / Tablet			Amount (%) / Tablet		
	Sacubitril and Valsartan Tablets 24 mg/ 26 mg	Sacubitril and Valsartan Tablets 49 mg / 51 mg	Sacubitril and Valsartan Tablets 97 mg/ 103 mg	Sacubitril and Valsartan Tablets 24 mg/ 26 mg	Sacubitril and Valsartan Tablets 49 mg / 51 mg	Sacubitril and Valsartan Tablets 97 mg/ 103 mg
Sacubitril and Valsartan						
Microcrystalline Cellulose (b)(4) USP-NF						
Crospovidone (b)(4) USP-NF						
Croscarmellose Sodium (b)(4) USP-NF						
Colloidal Silicon Dioxide (b)(4) USP-NF						
Talc (b)(4) USP						
Magnesium Stearate (b)(4) USP-NF						
(b)(4)						

⁴ EDR, A213748, \\CDSESUB\levsprod\anda213748\0005\m3\32-body-data\32p-drug-prod\sac-v\srtn-tab-msn-lab\32p1-desc-comp\description-and-composition.pdf.

(b)(4)									
Total	103.000	206.000	412.000	100.00	100.00	100.00	100.00	100.00	100.00

(b)(4)

DELETED PAGES INFORMATION SHEET

IT IS NOT REASONABLE TO SEGREGATE MEANINGFUL PORTIONS OF THE RECORD FOR RELEASE.

INFORMATION HAS BEEN WITHHELD IN ITS ENTIRETY IN ACCORDANCE WITH THE FOLLOWING EXEMPTIONS(S):

(b) (4)

5 U.S.C. 552 (b) (4) - trade secrets and commercial or financial information obtained from a person and privileged or confidential.

(b)(4)

Comments on Formulation: Acceptable

- The formulation of the test product, as tablet, was previously evaluated and found acceptable⁸. Since the suspension of test and reference products would be prepared same way per the RLD labeling using Ora-Plus® and Ora-Sweet® SF, from the IIG perspective, the assessor only evaluated the ingredients in the suspension agents which are common to the test formulation and determined whether the combined amount would exceed the IIG limit. The maximum daily intake (MDI) of other suspension agents should be the same for the test and reference products.

The assessor notes that the only ingredient common to the test formulation and Ora-Plus® and Ora-Sweet® SF is

(b)(4)

This is consistent with the approach used in BE assessment of another ANDA of the same drug product.

The RLD labeling includes Recommended Dose Titration table (please see table below). From this information, the assessor calculated the maximum daily dose (MDD,

⁶ IIG-MDD Master Spreadsheet located within the folder:

[//fda.gov/wodc/CDER/OGD/All/OGDS11/DIVISION/BIO/BIO2/IIG-MDD Spreadsheet:](https://fda.gov/wodc/CDER/OGD/All/OGDS11/DIVISION/BIO/BIO2/IIG-MDD%20Spreadsheet)

(b)(4)

(b)(4)

⁸ GDRP, BE assessment of the original submission,

<https://panorama.fda.gov/internal/document/preview?versionID=5e093a36010701ec64cba50816d97964&ID=5de99fbb002c8bc85574b04e53bbcd21>.

(b)(4), Please note that the dose of sacubitril and valsartan is also presented as combination of the two drug components per the RLD labeling. For example (b)(4)

(b)(4)

(b)(4)

Per the RLD labeling, to prepare for 200 mL suspension, 60 mL of Ora-Plus® and 140 mL of Ora-Sweet® SF are used. (b)(4)

(b)(4)

(b)(4) This is consistent with the approach used in BE assessment of another ANDA of the same drug product.

(b)(4)

The suspension formulation when prepared using Ora-Plus® and Ora-Sweet® SF does not pose safety concern from the IIG perspective hence is adequate.

-

(b)(4)

(b)(4)

Since the same amount of suspension agents are to be used for preparation of suspension for test and reference products, there is no safety concern for the test product with regard to methylparaben and propylparaben.

(b)(4)

- The formulation of suspension prepared from the test product is **acceptable**.

3 ADDITIONAL CONSIDERATION RELATED TO SUSPENSION OF TEST PRODUCT

The Draft *Guidance for Industry, Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* (Aug. 2021) states:

“If the labeling specifies that the product must be administered in a specific beverage or beverages, applicants should administer the product mixed with one of the beverages mentioned in the labeling for BE studies. If additional beverages are listed in the labeling, applicants should provide evidence that the use of these additional beverages would not result in BE differences.

If applicants have questions not addressed in the applicable PSG about the use of other vehicles or about the design or analysis of such BE studies, they should contact the Office of Generic Drugs via a controlled correspondence.”

The process of suspension preparation (i.e., crushing the tablets and suspending in Ora Plus and Ora Sweet) may be similar to mixing the drug product with a beverage. Nonetheless, in line with the discussion on 8/10/2021 within DBI for this drug product, at this time, no additional data will be requested from the applicant to support BE of the suspension of the test and reference products.

(b)(4)

(b)(4)

(b)(4)

BE has also been demonstrated for the tablets of the test and reference products; therefore, the risk is considered low.

NOTE TO REGULATORY PROJECT MANAGER: The bioequivalence assessment outcome does not change. No letter will be communicated to the applicant as result of this addendum.

There are three Policy Alerts related to this drug product: Citizen Petition (CP) # FDA-2019-P-1893 and FDA-2021-P-1286, for ENTRESTO® (sacubitril/valsartan) Tablets and CP FDA-2019-P-2869 for multiple valsartan products or drug products containing valsartan.

No Approval Actions (AP/TA) can be taken prior to contacting Policy Lead. All disciplines can continue communications (CRL, IR/DRL).

4 PRODUCTIVITY

Completed Assignment for 213748 ID: 47898

Reviewer:	Manerikar, Archana	Date Completed:
Verifier:	,	Date Verified:
Division:	Division of Bioequivalence Addendum assessment for Sacubitril and Valsartan	
Description:	Tablets, 24 mg/26 mg, 49 mg /51 mg and 97 mg/103 mg (A213748)	

Items:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Score</i>	<i>Subtotal</i>	
47898	4/8/2022	BIO	Addendum [1]	1	1	Edit Delete
47898	4/8/2022	Parallel	Addendum (not for Clarification or Error Correction) [1]	1	1	Edit Delete
Total:					2	

DIVISION OF BIOEQUIVALENCE ASSESSMENT

ANDA No.	213748			
Drug Product Name	Sacubitril; Valsartan Tablets*			
Strength(s)	24 mg; 26 mg, 49 mg; 51 mg, and 97 mg; 103 mg*			
Applicant Name	MSN Laboratories Private Limited			
Applicant Address	MSN House, Plot No. C-24, Industrial Estate, Sanath Nagar, Hyderabad 500018, Telangana, India			
US Contact Name and US Mailing Address	Dr. Kondal Reddy Bairy MSN Pharmaceuticals Inc. 20 Duke Road, Piscataway NJ 08854-3714			
US Contact Telephone Number	848-200-1906 kondal@msnlabs.com			
US Contact Fax Number	732-902-2113, 501-421-8200			
Original Submission Date(s)	07/08/2019 (SD1, Original ANDA Submission)			
Submission Date(s) of Amendment(s) Under Review	N/A			
Primary Reviewer	Archana Manerikar, Pharm.D., M.S.			
Secondary Reviewer	Amanda Jones, Ph.D.			
Tertiary Reviewer	N/A			
Study Number(s)	BA18647467	BA18647468	BA18647469	BA18647470
Study Type(s)	Pilot Fasting	Pilot Fed	Fasting	Fed
Strength(s)	97 mg (Sacubitril); 103 mg (Valsartan)			
Clinical Site	Cliantha Research Limited			
Clinical Site Address	Sigma-1 Corporate, B/H Rajpath Club, Opposite Mann Party Plot, Off. S.G. Highway, Bodakdev, Ahmedabad-380 054, Gujarat, India			
Analytical Site	(b)(4)			
Analytical Site Address				
Office of Study Integrity and Surveillance (OSIS) status	<u>Backlog, Year 1 and Year 2 ANDAs</u> ☐ Pending ☐ Complete		<u>Post October 1, 2014 ANDAs</u> ☒ To Be Determined by OSIS (Clinical Site) ☐ Pending For Cause Inspection ☒ Complete (Bioanalytical Site) ☐ N/A (Waiver/Deem Bioequivalent) ¹	

	☐ N/A (Waiver/Deem Bioequivalent) ¹		
Waiver/Deem Bioequivalent	☐ Granted ☐ Tentatively granted ☒ Not granted ☐ N/A		
QC Dissolution	☒ Pending ☐ Adequate ☐ Inadequate ☐ N/A		
Formulation	☒ Adequate ☐ Inadequate		
Will Response to CR Result in a Reformulation?	☐ Possibly ☐ No ☒ N/A		
Deficiency Classification	☐ Major ☒ Minor/IR ☐ N/A (Review is Adequate)		
Major Deficiency Theme	N/A		
Justification for Major Designation	N/A		
Overall Review Result	☐ Adequate ☒ Inadequate		
Product Specific Guidance (PSG) Referenced in Review	☒ Recommended/Latest Revision Date: <u>Apr 2016</u> RLD Number: <u>NDA 207620</u> ☐ N/A (no PSG available at time of review)		
Revised/New Draft Guidance Generated as Part of Current Review	☐ YES ☒ NO		
Bioequivalence study tracking/supporting document #	Study/test type	Strength	Review Result
1	Fasting	97 mg/103 mg	☐ Adequate ☒ Inadequate
1	Fed	97 mg/103 mg	☐ Adequate ☒ Inadequate
1	Waiver/Deem Bioequivalent	24 mg/26 mg, and 49 mg/51 mg	☐ Adequate ☒ Inadequate

* Please note that throughout this assessment, this drug product may be interchangeably referred to as Sacubitril/Valsartan Tablets, 24 mg/26 mg or 50 mg, 49 mg/51 mg or 100 mg, and 97 mg/103 mg or 200 mg.

¹ Requests submitted under 21 CFR 320.22(d)(2) or 320.24(b)(6).

1 EXECUTIVE SUMMARY

This is a *potential first* generic drug application.

This application contains the results of fasting and fed bioequivalence (BE) studies comparing the test product, MSN Laboratories Private Limited's Sacubitril and Valsartan Tablets, 97 mg/103 mg, to the corresponding reference product, Novartis Pharmaceuticals Corp.'s ENTRESTO™ (sacubitril and valsartan) Tablets, 97 mg/103 mg (NDA 207620, approved on July 7, 2015). Each of the BE studies was designed as a single-dose, two-treatment, three-sequence, three-period crossover, reference-scaled study in healthy male subjects. The applicant's fasting and fed BE studies are inadequate due to a deficiency related to SAS concentration dataset submission.

Due to incomplete raw concentration (SAS) datasets for both analytes and both pivotal studies as submitted by the applicant, the assessor's statistical determination of BE (i.e. SAS evaluation) for the pivotal studies is not conducted at this time and will be completed upon applicant's satisfactory response to the deficiency letter issued per the current assessment. Please see assessor's comments under the pharmacokinetic (PK) results sections for each pivotal study for further details.

The applicant calculated results for both analytes, Sacubitril (SAC) and Valsartan (VAL) are provided in the tables below.

Fasting Study (BA18647469):

SAC:

Sacubitril and Valsartan Tablets (No of subjects completed= 45) 1x 97 mg / 103 mg Least Square Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fasting Bioequivalence Study (BA18647469)						
Parameter	Test	N	RLD	N	Ratio	90%CI
AUCt (µg*hr/mL)	2.526	45	2.243	90	112.60%	NA
AUCi (µg*hr/mL)	2.558	45	2.414	88^	105.99%	(102.77%;109.32%)
Cmax (µg /mL)	1.897	45	1.818	90	104.33%	NA

Notes:-

NA = Not Applicable; within subject standard deviation of reference product (S_{WR}) of Cmax and AUCt were greater than 0.294. Hence, Scaled Average Bioequivalence approach was used to assess bioequivalence for Cmax and AUCt.

^ For Reference Product, Subject [] (Period-I) and Subject [] (Period-III) did not exhibit a terminal log-linear phase in the concentration versus time profile, so AUCi, AUC_%Extrap_obs, Kel & tHalf parameters were not estimated. Hence, N=88 instead of 90 for AUCi, AUC_%Extrap_obs, Kel & tHalf parameters.

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	Outcome
LAUCt	1.12^	NA	NA	0.3200	0.566	-0.1649	Scaled Average Bioequivalence	Bioequivalent
LAUCi	105.99%*	102.77%	109.32%	0.0049	0.070	NA	Average Bioequivalence	Bioequivalent

LCmax	1.04 [^]	NA	NA	0.2998	0.548	-0.1683	Scaled Average Bioequivalence	Bioequivalent
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Notes:-

* T/R ratio presented in percentage (%) of Unscaled average bioequivalence method.

[^]point estimate of Scaled average bioequivalence method as per protocol.

NA = Not Applicable

VAL:

Sacubitril and Valsartan Tablets (No of subjects completed= 45) 1x 97 mg / 103 mg Least Square Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fasting Bioequivalence Study (BA18647469)						
Parameter	Test	N	RLD	N	Ratio	90% CI
AUCt (µg*hr/mL)	26.164	45	27.612	90	94.76%	NA
AUCi (µg*hr/mL)	26.575	45	28.031	90	94.81%	NA
Cmax (µg /mL)	4.130	45	4.505	90	91.67%	NA

Note:-

NA = Not Applicable; The within subject standard deviation of reference product (S_{WR}) of Cmax, AUCt and AUCi were greater than 0.294. Hence, Scaled Average Bioequivalence approach was used to assess bioequivalence for Cmax, AUCt and AUCi.

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	Outcome
LAUCt	0.95	NA	NA	0.2217	0.471	-0.1190	Scaled Average Bioequivalence	Bioequivalent
LAUCi	0.95	NA	NA	0.2060	0.454	-0.1101	Scaled Average Bioequivalence	Bioequivalent
LCmax	0.92	NA	NA	0.2088	0.457	-0.1004	Scaled Average Bioequivalence	Bioequivalent

Note:- NA = Not Applicable

Fed Study (BA18647470):**SAC:**

Sacubitril and Valsartan Tablets (No of subjects completed= 45) 1x 97 mg / 103 mg Least Square Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fed Bioequivalence Study (BA18647470)						
Parameter	Test	N	RLD	N	Ratio	90% CI
AUCt (µg*hr/mL)	1.989	45	1.948	90	102.06%	(99.76%;104.42%)
AUCi (µg*hr/mL)	2.011	45	1.973	88 [^]	101.94%	(99.67%;104.26%)
Cmax (µg /mL)	1.163	45	1.129	90	103.03%	(95.20%;111.50%)

Notes: -

The within subject standard deviation of reference product (S_{WR}) of Cmax, AUCt and AUCi were less than 0.294. Hence, Average Bioequivalence approach was used to assess bioequivalence for Cmax, AUCt and AUCi parameters.

[^] For Reference Product, Subject [] (Period-I) and Subject [] (Period-II) did not exhibit a terminal log-linear phase in the concentration versus time profile, so AUCi, AUC_%Extrap_obs, Kel & tHalf parameters were not estimated. Hence, N=88 instead of 90 for AUCi, AUC_%Extrap_obs, Kel & tHalf parameters.

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	Outcome
LAUCt	102.06%	99.76%	104.42%	0.0038	0.062	NA	Average Bioequivalence	Bioequivalent
LAUCi	101.94%	99.67%	104.26%	0.0039	0.063	NA	Average Bioequivalence	Bioequivalent
LCmax	103.03%	95.20%	111.50%	0.0765	0.277	NA	Average Bioequivalence	Bioequivalent

Note:- NA = Not Applicable

VAL:

Sacubitril and Valsartan Tablets (No of subjects completed= 45) 1x 97 mg / 103 mg Least Square Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fed Bioequivalence Study (BA18647470)						
Parameter	Test	N	RLD	N	Ratio	90%CI
AUCt (µg*hr/mL)	16.597	45	16.532	90	100.39%	(94.84%;106.27%)
AUCi (µg*hr/mL)	16.964	45	16.888	90	100.46%	(95.01%;106.22%)
Cmax (µg /mL)	2.591	45	2.707	90	95.72%	(90.11%;101.67%)

Note: -

The within subject standard deviation of reference product (S_{WR}) of Cmax, AUCt and AUCi were less than 0.294. Hence, Average Bioequivalence approach was used to assess bioequivalence for Cmax, AUCt and AUCi parameters.

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	Outcome
LAUCt	100.39%	94.84%	106.27%	0.0197	0.140	NA	Average Bioequivalence	Bioequivalent
LAUCi	100.46%	95.01%	106.22%	0.0190	0.138	NA	Average Bioequivalence	Bioequivalent
LCmax	95.72%	90.11%	101.67%	0.0244	0.156	NA	Average Bioequivalence	Bioequivalent

Note:- NA = Not Applicable

Per the applicant's statistical analysis, in the pivotal fasting and fed studies, the test product was considered as bioequivalent to the reference product when the ln-transformed parameters Cmax, AUC_{0-t} (AUCt), and AUC_{0-inf} (AUCi) for SAC and VAL satisfy the following criteria for reference scaled average BE (RSABE) or average / unscaled BE (ABE) when within-subject standard deviation of reference formulation (S_{WR}) ≥ 0.294 or < 0.294 respectively:

RSABE approach:

- The 95% upper confidence bound for $(\mu_T - \mu_R)^2 - \theta * S^2_{WR}$ is ≤ 0 ;
- The point estimate (test/reference [T/R] geometric mean ratio) falls within [0.80, 1.25].

ABE Approach:

- 90% confidence interval (CI) for the geometric least squares mean ratio (T/R) for PK parameters, C_{max} , AUCT, and AUCI falls within the acceptance range of 0.80 to 1.25.

Per the applicant's statistical analysis for SAC in the fasting study, since SWR was ≥ 0.294 for C_{max} and AUCT but not for AUCI, BE based on C_{max} and AUCT was concluded using RSABE approach whereas that based on AUCI was concluded using ABE approach. For VAL, since SWR was ≥ 0.294 across the board, BE based on C_{max} , AUCT, and AUCI was concluded using RSABE approach. Per the applicant's statistical analysis, for the fed study, for both SAC and VAL, since SWR was < 0.294 for C_{max} , AUCT, and AUCI, BE for both analytes was concluded using ABE approach.

Test Formulation

The test product formulation is adequate with excipients within the limits of previously approved drug products indicated for use at maximum daily dose in all patient populations indicated per the RLD labeling. The biowaiver strengths of the test product (i.e. SAC/VAL 24 mg/26 mg, and SAC/VAL 49 mg/51 mg) are proportionally similar to the bio-study strength (i.e. SAC/VAL 97 mg/103 mg).

In Vitro Dissolution Analysis

The applicant conducted dissolution testing using their own dissolution test method (b)(4)

(b)(4) that is not the same as the FDA-recommended method [USP Type I Basket, pH 6.8 Phosphate buffer (b)(4) 75 RPM, 900 mL volume, 37.0°C temperature]². The dissolution data are currently inadequate with respect to supporting waiver request under 21 CFR 320.22 (d)(2) for the biowaiver test strengths. The Division of Bioequivalence I (DBI) denies the waiver request for in vivo BE study requirements for the biowaiver strengths of the test product (i.e. SAC/VAL 24 mg/26 mg, and SAC/VAL 49 mg/51 mg) based on criteria set forth in 21 CFR 320.22 (d)(2) due to inadequate pivotal BE studies and pending biopharmaceutics evaluation of the applicant's in-house dissolution method.

Pilot Studies

Two failed pilot studies were reported in this application: fasting study # BA18647467 and fed study # BA18647468. These studies used the same test product formulation as that used in the pivotal fasting and fed studies and there were no deaths or serious adverse events reported during study conduct (Please see section 4.4.1 for details).

The Office of Study Integrity and Surveillance (OSIS) Status

Per GDRP, the OSIS inspection status of the clinical site (Clantha Research Limited, Sigma-1 Corporate, B/H Rajpath Club, Opposite Mann Party Plot, Off. S.G. Highway, Bodakdev, Ahmedabad-380 054, Gujarat, India) is currently pending³.

² FDA Dissolution Database; search by "Sacubitril".

https://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_SearchResults.cfm Date Updated 12/4/2019.

³ GDRP-Clinical Site, <https://panorama.fda.gov/task/view?ID=5d23bd760014a74dc44555b7faf19a62>, last accessed: 12/05/2019.

The OSIS inspection status of the bioanalytical site

(b)(4)

(b)(4)

for the current ANDA is complete⁴. OSIS inspected the bioanalytical site in (b)(4) which falls within the surveillance interval with an outcome of No Action Indicated (NAI), and as a result of which an inspection is not warranted at this time.

In addition, the studies submitted in the current ANDA do not indicate any conduct issues and no data integrity deficiencies were identified by the assessor. The OSIS inspection status of the current ANDA is complete for the analytical site. However, the OSIS inspection status of the current ANDA is pending for the clinical site. Upon completion of the BE Site Inspection task by OSIS, the BE assessment team will evaluate the inspection outcome (per Establishment Inspection Report (EIR) or Decline to Inspect Memo).

The application is **inadequate** due to deficiency related to SAS concentration dataset submission for both analytes and both pivotal studies.

NOTE TO DBI PROJECT MANAGER and REGULATORY PROJECT MANAGER (RPM): As per OGD Policy, a Citizen Petition (CP) is pending for this drug product which states the following:

CP # FDA-2019-P-1893, for ENTRESTO® (sacubitril/valsartan) tablet requests FDA to: (1) Require ANDAs that reference ENTRESTO to demonstrate API sameness; (2) Revise FDA's Draft Guidance document regarding sacubitril/valsartan oral tablets to recommend that API sameness be established by showing that the chemical structure of each active ingredient in the finished dosage form of a proposed generic is identical to the chemical structure of each active ingredient in the RLD, including all ionic bonds; (3) Further revise the Draft Guidance to include BE and PK requirements.

Actions: No Approval Actions (AP/TA) can be taken prior to contacting Policy Lead.

Citizen petition (FDA-2019-P-2869) for Multiple drug products containing valsartan, which requests FDA to: 1) review and significantly lower the acceptable intake/permitted daily exposure limit of DMF, as listed in the current FDA guidance Q3C – Tables and List, Guidance for Industry, from its current level of 8,800,000 nanograms to less than 1,000 nanograms (and potentially as low as 96 nanograms); 2) request a recall of identified lots of valsartan on the basis that, due to contamination with a probable human carcinogen, these drugs are adulterated under Section 501 of the FDCA (21 U.S.C. § 351) and misbranded under Section 502 of the FDCA (21 U.S.C. § 352); 3) conduct examinations and investigation under Section 702 (a) of the FDCA (21 U.S.C. § 372(a)) regarding these products, their manufacturing processes, and the manufacturer submissions made for FDA approval under 704 (a) of the FDCA (21 U.S.C. § 374(a)) and effect labeling revisions as needed

Actions: No Approval Actions (AP/TA) can be taken prior to contacting Policy Lead.

⁴ GDRP-Bioanalytical Site,

<https://panorama.fda.gov/task/view?ID=5d275e6c003e6196da09b23409c98bce>, last accessed: 12/05/2019.

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3 SUBMISSION SUMMARY

3.1 Drug Product Information⁵

Test Drug Product and Strength(s)	Sacubitril and Valsartan Tablets, 97 mg/103 mg; 49 mg/51 mg; 24 mg/26 mg
Reference Standard (RS) and Strength(s)	ENTRESTO® (sacubitril/valsartan) Tablets, 97 mg/103 mg
RS Holder; NDA/ANDA Number; Approval Date	Novartis Pharmaceuticals Corp. NDA 207620; Jul 7, 2015
Reference Listed Drug (RLD) and Strength(s)	ENTRESTO® (sacubitril/valsartan) Tablets 24 mg/26 mg; 49 mg/51mg; 97 mg/103 mg
RLD Holder; NDA/ANDA Number; Approval Date	Same as RS

3.2 PK/PD Information⁶

Most recent RLD labeling	https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/207620s0131bl.pdf Revised October 2019
Indication	ENTRESTO is a combination of sacubitril, a neprilysin inhibitor, and valsartan, an angiotensin II receptor blocker (ARB) indicated: - 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 usually administered in conjunction with other heart failure therapies, in place of an angiotensin-converting enzyme (ACE) inhibitor or other ARB. - 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.
Boxed warning	- When pregnancy is detected, discontinue ENTRESTO as soon as possible. - Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus.
Bioavailability	The oral absolute bioavailability of sacubitril is estimated to be $\geq 60\%$. The valsartan in ENTRESTO is more bioavailable than the valsartan in other marketed tablet formulations; 26 mg, 51 mg, and 103 mg of valsartan in ENTRESTO is equivalent to 40 mg, 80 mg, and 160 mg of valsartan in other marketed tablet formulations, respectively.
Food Effect	ENTRESTO administration with food has no clinically significant effect on the systemic exposures of sacubitril, LBQ657, or valsartan. Although there is a

⁵ Electronic Orange Book

https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=207620#30823, last Accessed: 11/25/2019.

⁶ Drugs@FDA, Search Term: 012750, Action Date: 10/1/2019, Suppl-13;

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/207620s0131bl.pdf, last Accessed: 11/25/2019.

	decrease in exposure to valsartan when ENTRESTO is administered with food, this decrease is not accompanied by a clinically significant reduction in the therapeutic effect. ENTRESTO can therefore be administered with or without food.
Tmax	Sacubitril is further metabolized to LBQ657. The peak plasma concentrations of sacubitril, LBQ657, and valsartan are reached in 0.5 hours, 2 hours, and 1.5 hours, respectively.
Metabolism	Sacubitril is readily converted to LBQ657 by esterases; LBQ657 is not further metabolized to a significant extent. Valsartan is minimally metabolized; only about 20% of the dose is recovered as metabolites. A hydroxyl metabolite has been identified in plasma at low concentrations (< 10%).
Excretion	Following oral administration, 52% to 68% of sacubitril (primarily as LBQ657) and ~ 13% of valsartan and its metabolites are excreted in urine; 37% to 48% of sacubitril (primarily as LBQ657), and 86% of valsartan and its metabolites are excreted in feces.
Half-life	Sacubitril, LBQ657, and valsartan are eliminated from plasma with a mean elimination half-life (T _{1/2}) of approximately 1.4 hours, 11.5 hours, and 9.9 hours, respectively.
Maximum Daily Dose (MDD)	<u>Adult:</u> Sacubitril / Valsartan – 97/103 mg, twice daily (2 x 97/103 mg = 194 mg / 206 mg). <u>Pediatric:</u> • 50 kg or more: 97/103 mg, twice daily- i.e. MDD = 400 mg combined dose daily. • 40 to 49 kg: 72 mg/78 mg, twice daily (3 x 24/26 mg x 2 times daily = 144 mg / 156 mg) – i.e. MDD = 300 mg combined dose daily • Less than 40 kg: 3.1 mg/kg, twice daily (combined amount of Sacubitril / Valsartan, twice daily) [3.1 x 40 = 124 x 2 times daily = 248 mg combined Sacubitril / Valsartan daily which is equivalent to 2.5 x 49/51 tablet as used to prepare oral suspension recommended in pediatric patients less than 40 kg = 250 mg combined Sacubitril / Valsartan daily.] – i.e. MDD = 250 mg combined dose daily. Therefore, pediatric MDD for excipient justification = 400 mg combined dose daily. Safety and effectiveness have not been established in pediatric patients less than 1 year of age.
	(b)(4)

3.3 OGD Recommendations for Drug Product

Source of most recent recommendations	https://www.accessdata.fda.gov/drugsatfda_docs/psg/Sacubitril;%20Valsartan_oral%20tablet_RLD%20207620_RC04-16.pdf <i>Recommended Apr 2016⁷</i>	
Summary of OGD or DB History	Approved ANDAs ⁸ :	None
	Pending ANDAs ⁹ :	Multiple, besides the current ANDA.  ANDA by RLD Search_11252019.pd
	Controls ¹⁰ :	Yes, multiple (One from current applicant – CC# 00981 ¹¹ (dated 11/26/2018) - The applicant sought the Agency's recommendation on acceptability of a generic formulation containing a physical mixture of Sacubitril and Valsartan in a ratio of 1: 1 as individual drug substances for all three equivalent strengths and also whether the proposed drug may be filed as ANDA [505 (j)] or NDA [505(b)(2)].
	Protocols ^{12, 13} :	None
	Pending Citizen Petitions and other legal and regulatory issues: If yes, please comment.	☒ Yes ¹⁴ ☐ No See comments below.

Two Citizen Petitions were documented:

1. **Citizen petition (FDA-2019-P-1893)** for ENTRESTO® (sacubitril/valsartan) Tablet requests FDA to: (1) Require ANDAs that reference ENTRESTO to demonstrate API sameness; (2) Revise FDA's Draft Guidance document regarding sacubitril/valsartan oral tablets to recommend that API sameness be established by showing that the chemical structure of each active ingredient in the finished dosage

⁷ Product Specific Guidance (PSG),

https://www.accessdata.fda.gov/drugsatfda_docs/psg/Sacubitril;%20Valsartan_oral%20tablet_RLD%20207620_RC04-16.pdf.

⁸ Electronic Orange Book, Search Term: Sacubitril,

https://www.accessdata.fda.gov/scripts/cder/ob/search_product.cfm; last Accessed: 11/25/2019.

⁹ GDRP; Search Term: NDA 207620, last accessed 11/25/2019.

¹⁰ GDRP and Mercado; Search Terms: Entresto, Sacubitril, Valsartan; last accessed 10/25/2019.

¹¹ GDRP, <http://panorama.fda.gov/project/view?ID=5c067ff0002d4b40ee1133567522260e>.

¹² GDRP; Search Term: Entresto; last accessed 10/25/2019.

¹³ Protocols Tracking, Search Terms: Sacubitril, Valsartan; <http://ogd.fda.gov/seltrack/ProtocolGrid.ASP>; last accessed 10/25/2019.

¹⁴ OGD Policy Alert List -As of 12022019, <http://sharepoint.fda.gov/orgs/CDER-OGD/OGDP/OGD%20Policy%20Alert/SitePages/Home.aspx>; last accessed 11/25/2019.

form of a proposed generic is identical to the chemical structure of each active ingredient in the RLD, including all ionic bonds; (3) Further revise the Draft Guidance to include BE and PK requirements.

The recommended approval action: No Approval Actions (AP/TA) can be taken prior to contacting Policy Lead.

2. **Citizen petition (FDA-2019-P-2869)** for Multiple drug products containing valsartan, which requests FDA to: 1) review and significantly lower the acceptable intake/permitted daily exposure limit of drug master file (DMF), as listed in the current FDA guidance Q3C – Tables and List, Guidance for Industry, from its current level of 8,800,000 nanograms to less than 1,000 nanograms (and potentially as low as 96 nanograms); 2) request a recall of identified lots of valsartan on the basis that, due to contamination with a probable human carcinogen, these drugs are adulterated under Section 501 of the FDCA (21 U.S.C. § 351) and misbranded under Section 502 of the FDCA (21 U.S.C. § 352); 3) conduct examinations and investigation under Section 702 (a) of the FDCA (21 U.S.C. § 372(a)) regarding these products, their manufacturing processes, and the manufacturer submissions made for FDA approval under 704 (a) of the FDCA (21 U.S.C. § 374(a)) and effect labeling revisions as needed.

The recommended approval action: No Approval Actions (AP/TA) can be taken prior to contacting Policy Lead.

3.4 Pre-Study Bioanalytical Method Validation

Information Requested	Data for Sacubitril (SAC)	Data for Valsartan (VAL)
Bioanalytical (BA) method validation report (MVR) location	Module 5/ Section 5.3.1.4/ Attachment 6(i) / Method Validation Report / Page 01 to 144	Module 5/ Section 5.3.1.4/ Attachment 6(i) / Method Validation Report / Page 01 to 144
Analyte	Sacubitril	Valsartan
Internal standard (IS)	Sacubitril D4	Valsartan D9
Method description	(b)(4)	
Limit of quantitation	0.01000 µg/mL	0.02000 µg/mL
Average recovery of drug (% , CV %)	LQC: 93.9 MQC2: 92.7 MQC1: 92.2 HQC: 94.2 Overall: 93.3 (1.0)	LQC: 91.0 MQC2: 90.9 MQC1: 90.4 HQC: 92.0 Overall: 91.1 (0.7)
Average recovery of IS (%)	107	95.6
Standard curve concentrations (µg /mL)	0.01000, 0.02000, 0.04000, 0.1000, 0.3000, 0.6000, 1.200, 2.400, 4.800 and 6.000	0.02000, 0.04000, 0.08000, 0.2000, 0.6000, 1.200, 2.400, 4.800, 9.600 and 12.00
QC concentrations (µg /mL)	LQC: 0.03000, MQC-2: 0.3600, MQC-1: 2.100 and HQC: 4.500	LQC: 0.06000, MQC-2: 0.7200, MQC-1: 4.200 and HQC: 9.000
QC Intraday precision range (%)	0.6 to 3.6 (Intra-run)	0.9 to 3.5 (Intra-run)
QC Intraday accuracy range (%)	93.6 to 111 (Intra-run)	94.1 to 107 (Intra-run)
QC Interday precision range (%)	1.1 to 2.9 (Inter-run)	1.3 to 3.3 (Inter-run)
QC Interday accuracy range (%)	96.1 to 109 (Inter-run)	95.9 to 105 (Inter-run)
Bench-top stability (hrs)	27 hours at room temperature (15°C to 30°C) (For Sacubitril)	27 hours at room temperature (15°C to 30°C) (For Valsartan)
	27 hours at room temperature (15°C to 30°C) [For Sacubitril fortified with Metabolite Sacubitrilat (LBQ657) and 4-Hydroxy Valsartan (6.000/12.00 µg/mL)]	27 hours at room temperature (15°C to 30°C) [For Valsartan fortified with Metabolite Sacubitrilat (LBQ657) and 4-Hydroxy Valsartan (6.000/12.00 µg/mL)]
Stock stability (days)	34 days for Sacubitril and for Sacubitril D4 at refrigerator temperature (2°C to 10°C)	34 days for Valsartan and 11 days for Valsartan D9 at refrigerator temperature (2°C to 10°C)

Processed stability (hrs)	121 hours at room temperature (15°C to 30°C) and at refrigerator temperature (2°C to 10°C) (For Sacubitril) 124 hours at room temperature (15°C to 30°C) and 123 hours at refrigerator temperature (2°C to 10°C) [For Sacubitril fortified with Metabolite Sacubitril (LBQ657) and 4-Hydroxy Valsartan (6.000/12.00 µg/mL)]	121 hours at room temperature (15°C to 30°C) and at refrigerator temperature (2°C to 10°C) (For Valsartan) 124 hours at room temperature (15°C to 30°C) and 123 hours at refrigerator temperature (2°C to 10°C) [For Valsartan fortified with Metabolite Sacubitril (LBQ657) and 4-Hydroxy Valsartan (6.000/12.00 µg/mL)]
Freeze-thaw stability (cycles)	6 freeze thaw cycles (For Sacubitril) 6 freeze thaw cycles [For Sacubitril fortified with Metabolite Sacubitril (LBQ657) and 4-Hydroxy Valsartan (6.000/12.00 µg/mL)]	6 freeze thaw cycles (For Valsartan) 6 freeze thaw cycles [For Valsartan fortified with Metabolite Sacubitril (LBQ657) and 4-Hydroxy Valsartan (6.000/12.00 µg/mL)]
Long-term storage stability (days)^a	273 days at -20°C ± 10°C temperature (For Sacubitril) 274 days at -20°C ± 10°C temperature [For Sacubitril fortified with Metabolite Sacubitril (LBQ657) and 4-Hydroxy Valsartan (6.000/12.00 µg/mL)]	273 days at -20°C ± 10°C temperature (For Valsartan) 274 days at -20°C ± 10°C temperature [For Valsartan fortified with Metabolite Sacubitril (LBQ657) and 4-Hydroxy Valsartan (6.000/12.00 µg/mL)]
Dilution integrity	48.00 µg/mL, diluted to 10 times 9.000 µg/mL, diluted to 02 times	96.00 µg/mL, diluted to 10 times 18.00 µg/mL, diluted to 02 times
Selectivity	No significant interfering peak noted in blank plasma samples	No significant interfering peak noted in blank plasma samples

^a Addendum 2 to Method Validation Report (MVR)

SOP for bioanalytical method validation submitted?	☒ Yes ☐ No
Is the same anticoagulant used in the pre-method validation study and BE sample analysis? If not, was cross validation study conducted?	☒ Yes ☐ No K2 EDTA in human plasma
Does the duration of the each of the LTSS stability parameters support the sample preparation/assay duration and clinical study sample storage temperature?	☒ Yes ☐ No LTSS: <u>SAC and VAL</u> : 274 days at -20°C ± 10°C [in presence of metabolite Sacubitril (LBQ657) and 4-Hydroxy Valsartan Fasting: <u>SAC and VAL</u> : 28 days at -20°C ± 7°C Fed: <u>SAC and VAL</u> : 27 days at -20°C ± 10°C
Was the % recovery consistent across QC concentrations?	☒ Yes ☐ No
Was the pre-study validation of the bioanalytical method used for the pivotal bioequivalence studies acceptable?	☒ Yes ☐ No

Comments on the Pre-Study Method Validation: Adequate

1. Per MVR, the applicant stated that cross specificity experiment was performed to evaluate the interference between Sacubitril (SAC), Valsartan (VAL) and internal standards (ISTDs) and interference from Metabolite Sacubitrilat (LBQ657) and 4-Hydroxy Valsartan (b)(4) and that no significant interference was observed between SAC, VAL and the ISTDs. No significant interference of Metabolite Sacubitrilat (LBQ657) and 4-Hydroxy Valsartan was observed at the retention time of SAC, VAL and the ISTDs.
2. During the validation, interference check due to common medications such as Acetaminophen, Aspirin, Ibuprofen, Nicotine, Cetirizine, Caffeine, Ranitidine, Ondansetron and Diclofenac was evaluated under Sacubitril (SAC) and Valsartan (VAL) assay conditions. No significant interference was observed at the retention time of SAC, VAL and the internal standards (IS).

The assessor notes that the results (tabular result data) were not provided for the interference check and cross specificity experiments.

3.5 In Vivo Studies

Summary of all in vivo Bioequivalence Studies

Sacubitril (SAC) - Fasting Study:

Study Ref. No.	Study Objective	Study Design	Treatment (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (range))	(Mean Parameters $\pm$ SD) (% CV)						Study Report Location
					Cmax ($\mu\text{g/mL}$)	Tmax (hr)	AUCt ($\mu\text{g}\cdot\text{hr/mL}$)	AUCi ($\mu\text{g}\cdot\text{hr/mL}$)	tHalf (hr)	Kel (1/hr)	
Study # BA186 47469	- To evaluate the oral bioavailability of Sacubitril and Valsartan Tablets 97 mg/103 mg with that of 'ENTRESTO™' (Sacubitril and Valsartan) Tablets 97 mg/103 mg in healthy, adult, human subjects under fasting conditions. - To monitor the safety of the subjects.	An open label, randomized, two-period, three-sequence, reference replicated, crossover, balanced, single dose oral bioequivalence study.	Test Product T: Sacubitril and Valsartan Tablets 97 /103 mg, 1 $\times$ 97 mg / 103 mg, Oral, [Batch No.: DT1812070B]	48 dosed, 45 completed study (45 males) Age: 35 (22-44) years Healthy male subjects.	2.161 $\pm$ 1.162 (53.754)	0.500 (0.333- 5.000)	2.603 $\pm$ 0.708 (27.193)	2.636 $\pm$ 0.702 (26.633)	0.890 $\pm$ 0.379 (42.559)	0.872 $\pm$ 0.255 (29.268)	Module 5.3.1.2 Page no. 01 to 135 of study report
			Reference Product R: ENTRESTO™ (Sacubitril /Valsartan) Tablets 97 mg/103 mg, 1 $\times$ 97 mg / 103 mg, Oral, [Lot No.: FX000287]		2.040 $\pm$ 0.824 (40.412)	0.500 (0.333 -5.000)	2.429 $\pm$ 0.718 (29.569)	2.487 $\pm$ 0.675 (27.139)	0.854 $\pm$ 0.287 (33.594)	0.886 $\pm$ 0.247 (27.839)	

Notes:

- The mean age is calculated based on completed subjects. Tmax is presented as Median (Range).
- For Reference Product, Subject [] (Period-I) and Subject [] (Period-III) did not exhibited a terminal log-linear phase in the concentration versus time profile, so AUCi, AUC_%Extrap_obs, Kel & tHalf parameters were not estimated. Hence, N=88 instead of 90 for AUCi, AUC_%Extrap_obs, Kel & tHalf parameters.

Valsartan (VAL) - Fasting Study:

Study Ref. No.	Study Objective	Study Design	Treatment (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (range))	(Mean Parameters $\pm$ SD) (%CV)						Study Report Location
					Cmax ($\mu\text{g/mL}$)	Tmax (hr)	AUCt ($\mu\text{g}\cdot\text{hr/mL}$)	AUCi ($\mu\text{g}\cdot\text{hr/mL}$)	tHalf (hr)	Kel (1/hr)	
Study # BA1864 7469	- To evaluate the oral bioavailability of Sacubitril and Valsartan Tablets 97 mg/103 mg with that of 'ENTRESTO™' (Sacubitril and Valsartan) Tablets 97 mg/103 mg in healthy, adult, human subjects under fasting conditions. - To monitor the safety of the subjects.	An open label, randomized, three-period, two-treatment, three-sequence, reference replicated, crossover, balanced, single dose oral bioequivalence study.	Test Product T: Sacubitril and Valsartan Tablets 97 mg/103 mg, 1 $\times$ 97 mg / 103 mg, Oral, [Batch No.: DT1812070B]	48 dosed, 45 completed study (45 males) Age: 35 (22-44) years Healthy male subjects.	4.563 $\pm$ 1.867 (40.920)	1.500 (1.000-3.500)	28.802 $\pm$ 12.031 (41.772)	29.167 $\pm$ 12.079 (41.414)	6.648 $\pm$ 1.895 (28.509)	0.112 $\pm$ 0.031 (27.677)	Module 5.3.1.2 Page no. 01 to 135 of study report
			Reference Product R: ENTRESTO™ (Sacubitril /Valsartan) Tablets 97 mg/103 mg, 1 $\times$ 97 mg / 103 mg, Oral, [Lot No.: FX000287]				30.334 $\pm$ 10.692 (35.249)	30.702 $\pm$ 10.737 (34.972)	6.777 $\pm$ 1.654 (24.412)	0.108 $\pm$ 0.028 (26.012)	

Note: The mean age is calculated based on completed subjects. Tmax is presented as Median (Range).

Sacubitril (SAC) - Fed Study:

Study Ref. No.	Study Objective	Study Design	Treatment (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (range))	(Mean Parameters $\pm$ SD) (%CV)						Study Report Location
					Cmax ($\mu\text{g/mL}$)	Tmax (hr)	AUCt ($\mu\text{g}\cdot\text{hr/mL}$)	AUCi ($\mu\text{g}\cdot\text{hr/mL}$)	tHalf (hr)	Kel (1/hr)	

Study # BA186 47470	- To evaluate the oral bioavailability of Sacubitril and Valsartan Tablets 97 mg/103 mg with that of 'ENTRESTO™' (Sacubitril and Valsartan) Tablets 97 mg/103 mg in healthy, adult, human subjects under fed conditions. - To monitor the safety of the subjects.	An open label, randomized, three-period, two-treatment, three-sequence, reference replicated, crossover, balanced, single dose oral bioequivalence study	Test Product T: Sacubitril and Valsartan Tablets 97 /103 mg, 1× 97 mg / 103 mg, Oral, [Batch No.: DT1812070B]	48 dosed, 45 completed study (45 males)	1.265 ±0.524 (41.395)	1.750 (0.500-4.500)	2.022 ±0.357 (17.644)	2.045 ±0.358 (17.531)	0.852 ±0.245 (28.724)	0.870 ±0.215 (24.724)	
			Reference Product R: ENTRESTO™ (Sacubitril /Valsartan) Tablets 97 mg/103 mg, 1× 97 mg / 103 mg, Oral, [Lot No.: FX000287]	Age: 32 (18-44) years Healthy male subjects.	1.231 ±0.539 (43.818)	1.775 (0.500-5.000)	1.987 ±0.380 (19.141)	2.008 ±0.379 (18.887)	0.798 ±0.315 (39.409)	0.954 ±0.253 (26.535)	
Module 5.3.1.2 Page no. 01 to 143 of study report											

Notes:

- The mean age is calculated based on completed subjects. Tmax is presented as Median (Range).
- For Reference Product, Subject - (Period-I) and Subject - (Period-II) did not exhibited a terminal log-linear phase in the concentration versus time profile, so AUCi, AUC_%Extrap_obs, Kel & tHalf parameters were not estimated. Hence, N=88 instead of 90 for AUCi, AUC_%Extrap_obs, Kel & tHalf parameters.

Valsartan (VAL) - Fed Study:

Study Ref. No.	Study Objective	Study Design	Treatment (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (range))	(Mean Parameters ± SD) (%CV)					Study Report Location
					Cmax (µg/mL)	Tmax (hr)	AUCt (µg*hr/mL)	AUCi (µg*hr/mL)	tHalf (hr)	Kel (1/hr)

Study # BA186 47470	- To evaluate the oral bioavailability of Sacubitril and Valsartan Tablets 97 mg/103 mg with that of 'ENTRESTO™' (Sacubitril and Valsartan) Tablets 97 mg/103 mg in healthy, adult, human subjects under fed conditions. - To monitor the safety of the subjects.	An open label, randomized, three-period, two-treatment, three-sequence, reference replicated, crossover, balanced, single dose oral bioequivalence study	Test Product T: Sacubitril and Valsartan Tablets 97 /103 mg, 1× 97 mg / 103 mg, Oral, [Batch No.: DT1812070B]	48 dosed, 45 completed study (45 males) Age: 32 (18-44) years Healthy male subjects.	2.702 ±0.828 (30.641)	3.000 (1.250-5.000)	17.419 ±5.754 (33.036)	17.785 ±5.814 (32.689)	7.224 ±2.580 (35.722)	0.106 ±0.032 (30.415)	Module 5.3.1.2 Page no. 01 to 143 of study report
			Reference Product R: ENTRESTO™ (Sacubitril /Valsartan) Tablets 97 mg/103 mg, 1× 97 mg / 103 mg, Oral, [Lot No.: FX000287]		2.824 ±0.823 (29.150)	3.667 (1.250-5.000)	17.320 ±5.535 (31.959)	17.672 ±5.576 (31.551)	6.777 ±2.180 (32.169)	0.112 ±0.033 (29.137)	

Note: The mean age is calculated based on completed subjects. Tmax is presented as Median (Range).

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-Dose Fasting Bioequivalence Study

4.1.1.1 Study Design

4.1.1.1.1 Study Information

Study Number	BA18647469	
Study Title	Single dose oral bioequivalence study of Sacubitril and Valsartan Tablets 97 mg/103 mg and 'ENTRESTO™' (Sacubitril and Valsartan) Tablets 97 mg/103 mg in healthy adult human subjects under fasting conditions.	
Clinical Site (Name & Address)	Clantha Research Limited Sigma-1 Corporate, B/H Rajpath Club, Opposite Mann Party Plot, Off. S.G. Highway, Bodakdev, Ahmedabad-380 054, Gujarat, India	
Principal Clinical Investigator	Dr. Mayur Soni, MBBS msoni@clantha.in & pi@clantha.in	
Dosing Dates	Period-I (P1): 5/2/2019 Period-II (P2): 5/10/2019 Period-III (P3): 5/18/2019	
Analytical Site (Name & Address)	(b)(4)	
Analysis Dates	05/21/2019 to 05/30/2019	
Principal Analytical Investigator	(b)(4)	
Sample Storage : (a) Duration (no. of days from the first day of sample collection to the last day of sample analysis) (b) Temperature Range (e.g., -20°C to -80°C)	(For Sacubitril and Valsartan) (a) 28 days (b) -20°C ± 10°C temperature (Clinical site) -20°C ± 7°C temperature (Analytical site)	
Long-Term Storage Stability (LTSS) Coverage (no. days @ temp °C)	(For Sacubitril and Valsartan) 273 days at -20°C ± 10°C temperature [For Sacubitril and Valsartan fortified with Metabolite Sacubitril at (LBQ657) and 4-Hydroxy Valsartan (6.000/12.00 µg/mL)] 274 days at -20°C ± 10°C temperature LTSS study reports and data are presented in Module 5/Section 5.3.1.4/ Attachment 6-3/ Addendum-II to the Method Validation Report/ Section 2.1/ Page 8 (For Sacubitril and Valsartan)	

	LTSS study reports and data are presented in Module 5/Section 5.3.1.4/ Attachment 6-3/ Addendum-II to the Method Validation Report/ Section 2.2/ Page 8 [For Sacubitril and Valsartan fortified with Metabolite Sacubitril at (LBQ657) and 4-Hydroxy Valsartan (6.000/12.00 µg/mL)]
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4.1.1.1.2 Product (Bio-batch) Information

Product	Test		RLD
Treatment ID	T		R
Product Name	Sacubitril and Valsartan Tablets 97 /103 mg		ENTRESTO™ (Sacubitril /Valsartan) Tablets 97 mg/103 mg
Manufacturer	MSN Laboratories Private Limited, Formulations Division, Unit-II Survey Nos. 1277 , 1319 to 1324, Nandigama (Village & Mandal), Ranga Reddy District Pin Code-509228, Telangana, India		(b)(4)
Batch/Lot No.	Batch No.: DT1812070B [§]		Lot No.: FX000287
Manufacture Date	Dec 2018		
Expiration Date			Jan 2021
Strength	97 mg/103 mg		97 mg/103 mg
Dosage Form	Tablet		Tablet
Bio-Batch Size	(b)(4)		
Production Batch Size			
Potency	Sacubitril: 103.2% Valsartan: 102.0%		Sacubitril: 99.1% Valsartan: 99.2%
Content Uniformity (mean, %CV) Chlordiazepoxide hydrochloride Clidinium bromide [^]	Sacubitril: Mean:103.20 % CV:1.08	Valsartan: Mean:102.00 % CV:1.08	
Dose Administered	1 × 97 mg/103 mg		1 × 97 mg/103 mg
Route of Administration	Oral		Oral

(b)(4)

¹⁵ GS Review: ANDA 213748, [\\cdsesub1\evsprod\anda213748\0000\m3\32-body-data\32p-drug-prod\sac-vlsrtn-tab-msn-lab\32p8-stab\stability-summ.pdf](#).

ANDA 213748
Single-Dose Fasting Bioequivalence Study Review

^The BE summary table in Module 2.7 states content uniformity as mean and %CV. However, this information is not in the certificate of analysis (CoA). Per the CoA, the acceptance values of sacubitril and valsartan are 4.4 and 3.2, respectively.

Are the test and reference products expired at the time of study? If Yes, please comment.	☐ Yes ☒ No
Is same bio-batch used in the dissolution and all BE studies? If No, please comment.	☒ Yes ☐ No
Is the bio-batch size at least the recommended minimum of 100K or 10% of the production batch (whichever is greater) for oral solid dosage form? If No, please comment.	☒ Yes ☐ No
Is difference of the potency values for the Test and RLD within 5%? If No, please comment.	☒ Yes, for SAC and VAL ☐ No

4.1.1.1.3 Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	Enrolled: 48 + 4 extra subjects [REDACTED] Dosed: 48 (Period 01, P1), 46 (Period 02, P2), 45 (Period 03, P3) Completed: 45 (Subject [REDACTED] replaced with extra subject [REDACTED] [REDACTED] replaced with extra subject [REDACTED] – extra subjects [REDACTED] were not dosed; [REDACTED] were discontinued) Samples Analyzed: 48 (45 completed and 03 discontinued subjects) Statistically Analyzed: 45
No. of Sequences	3
No. of Periods	3
No. of Treatments	2
No. of Groups	1
Washout Period	08 days
Randomization	☒ Yes ☐ No
Blood Sampling Times	Pre-dose (0.0 hour) and at 0.167, 0.333, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.333, 2.667, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0, 36.0, and 48.0 hours post dose in each period.
IRB Approval	☒ Yes Date: [REDACTED] ☐ No Date: 09/25/2018 (version 01) IRB approval predates period 01 dosing (05/02/2019).
Informed Consent	☒ Yes ☐ No Date: 09/25/2018 (version 01, English and Gujarati)
Length of Fasting	At least 10 hours prior to dosing until at least 04 hours post-dose in each period.
Length of Confinement	At least 11 hours prior to dosing until at least 48 hours post dose in each period.

Was the drug product administered per labeling for specialized dosage forms e.g. ODT)?	☐ Yes ☐ No ☒ N/A
Safety Monitoring	☒ Yes ☐ No

Comments on Study Design: Adequate

1. As noted in the section 3.2 of this assessment, considering SAC and VAL Tmax of 0.5 hours and 1.5 hours, respectively, and half-lives of 1.4 hours and 9.9 hours, respectively, the blood sampling time durations per study protocol for both fasting and fed studies through 48 hours for VAL and through 12 hours for SAC are sufficient to capture the absorption phase, Cmax, and the elimination phase for both analytes. The 8-day (fasting study) and 6-day (fed study) washout between study periods is sufficient to allow the elimination of both analytes prior to the next period. Additionally, the assessor verified that there are no instances of first time point Cmax for either analyte.
2. Per study protocol, subjects completing all periods (n=45) were included in BE evaluation with unscaled average BE (ABE) or reference scaled average bioequivalence (RSABE) method depending on the observed within subject variability of reference product (SWR) for each primary pharmacokinetic (PK) parameter. Per applicant, of the subjects to be included in the PK and statistical analysis per protocol, the subjects who completed two periods with reference treatment (n=45) and completed the study were included to estimate the SWR. For SAC, since SWR was ≥ 0.294 for Cmax and AUC_{0-t} (AUCT) but not for AUC_{0-inf} (AUCI), BE based on Cmax and AUCT was concluded using RSABE approach whereas that based on AUCI was concluded using ABE approach. For VAL, since SWR was ≥ 0.294 for all PK parameters, BE based on Cmax, AUCT, and AUCI was concluded using RSABE approach. The study design and statistical analysis approach are acceptable.

4.1.1.2 Clinical Results

4.1.1.2.1 Demographic Profile of Subjects

Study No. BA18647469			
		Treatment Groups	
		Test Product (T) N = 45	Reference Product (R) N = 45
Age (years)	Mean $\pm$ SD	35 ($\pm$ 6)	35 ($\pm$ 6)
	Range	22 - 44	22 - 44
Age Groups	< 18	00 (0%)	00 (0%)

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	18 – 40	39 (86.67%)	39 (86.67%)
	41 – 64	06 (13.33%)	06 (13.33%)
	65 – 75	00 (0%)	00 (0%)
	> 75	00 (0%)	00 (0%)
Sex	Male	45 (100%)	45 (100%)
	Female	00 (0%)	00 (0%)
Race	Asian	45 (100%)	45 (100%)
	Black	00 (0%)	00 (0%)
	Caucasian	00 (0%)	00 (0%)
	Hispanic	00 (0%)	00 (0%)
	Other	00 (0%)	00 (0%)
BMI (Kg/m ²)	Mean ± SD	23.5 (± 3.1)	23.5 (± 3.1)
	Range	18.6 - 29.6	18.6 - 29.6

Is the demographics profile of subjects completing the bioequivalence study in agreement with the current drug product recommendation? If no, please comment.	☒ Yes ☐ No
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4.1.1.2.2 Dropout Information

Study No. BA18647469				
Subject No	Reason for dropout/replacement	Period	Replaced?	Replaced with
(b)(6)	Reason: Withdrawal by subject. Date: (b)(6) Time: 0648 hours	NA	Yes	(b)(6)
	Reason: Withdrawal by subject. Date: (b)(6) Time: 0651 hours	NA	Yes	
	Reason: Protocol Violation (Subject found alcohol breath test positive during period-III check in) Date: (b)(6) Time: 1232 hours	Period II	No	NA

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	Last Treatment Received: Reference			
(b)(6)	Reason: Did not report for subsequent periods of the study. Date: Time: 1945 hours Last Treatment Received: Reference	Period I	No	NA
	Reason: Did not report for subsequent periods of the study. Date: Time: 1949 hours Last Treatment Received: Reference	Period I	No	NA

NA: Not applicable

Are dropouts appropriate? If no, please comment.	☒ Yes, the reviewer verified this information from the Case Report Forms (CRFs) ☐ No
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4.1.1.2.3 Study Adverse Events

(1) Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Fasted Bioequivalence Study Study No. BA18647469	
	Test (T) (2) N=45 (3) n (%)	Reference (R) (2) N=48 (3) n (%)
Investigations		
Alanine Aminotransferase Increased	-	02 (4.17%)
Aspartate Aminotransferase Increased	-	01 (2.08%)
White blood cell count Increased	-	01 (2.08%)
Total	00 (0.00%)	04 (8.33%)

(1) MedDRA Version 22.0

(2) N=Number of subjects dosed for each treatment

(3) n= Number of subjects reporting at least one incidence of respective adverse event; (%)=percentage of subjects reporting at least one incidence of respective adverse event

Were subjects who experienced vomiting included in statistical analysis?	☐ Yes ☐ No ☒ N/A
If yes, does the time of emesis exceed two times the median Tmax value (IR products) or the labeled dosing interval (MR products)? Please comment.	☐ Yes ☐ No ☒ N/A
Was the adverse event profile observed comparable for the test and reference product?	☒ Yes ☐ No

Are there any serious adverse events or death?	☐ Yes ☒ No
If yes, then if the study conducted in US, are they reported to the OGD Safety Committee?	☐ Yes ☐ No ☒ N/A
Are there any other safety concerns based on the adverse event profile?	☐ Yes ☒ No

4.1.1.2.4 Protocol Deviations

Study No. BA18647469		
Type	Subject #s (Test) (T)	Subject #s (Reference) (R)
Blood draw time point deviations, Period I	(b)(6)	
Blood draw time point deviations, Period II		
Blood draw time point deviations, Period III		

Note: Superscript above the subject number indicates the number of multiple occurrences of the indicated deviation recorded by that subject.

If the firm used nominal time points, the sampling time deviations (if any) > 5% and 90% CI of any PK parameters is border line, please reanalyze data using actual sampling time.	☒ Actual ☐ Nominal
--	---

Is the dropout/withdrawal/exclusion of subjects and protocol deviations as per the criteria mentioned in the IRB approved study protocol?	☒ Yes ☐ No
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Comments on Clinical Results: Adequate

1. Post-dose sampling time deviations are not likely to affect study outcome since actual sampling time points are provided in the dataset used for BE determination.
2. No concomitant medications were administered to the subjects during the study.

4.1.1.3 Bioanalytical Results

4.1.1.3.1 SOPs dealing with Sample Analysis including Repeat Analysis

SOP No.	Effective Date of SOP	SOP Title
(b)(4)		Sample Reanalysis and reporting criteria
		Bioanalytical Assay Method Validation
		Bioanalytical Assay Method Validation
		Performance Assessment of LC/MS/MS and ICP OES Systems
		Sample Analysis

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(b)(4)	Review of Analytical Run / Experiment
	Incurred Sample Reanalysis

All necessary SOPs submitted?	☒ Yes ☐ No
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4.1.1.3.2 Sample Analysis Calibration and Quality Control

Bioequivalence Study No.BA18647469 Sacubitril										
Parameter	Standard Curve Samples									
Concentration (µg/mL)	0.01000	0.02000	0.04000	0.1000	0.3000	0.6000	1.200	2.400	4.800	6.000
* Inter day Precision (%CV)	1.5	2.9	3.8	2.3	2.6	1.5	2.6	1.9	2.6	2.6
* Inter day Accuracy (%Actual)	97.9	102	103	104	102	101	99.9	98.5	97.3	94.9
Linearity (r ² value)	0.9960956 – 0.9994451									
Linearity Range (µg/mL)	0.01000 – 6.000									
Sensitivity /LOQ (µg/mL)	0.01000									
Bioequivalence Study No.BA18647469 Sacubitril										
Parameter	Quality Control Samples									
Concentration (µg/mL)	LQC 0.03000		MQC-2 0.3600		MQC-1 2.100			HQC 4.500		
* Inter day Precision (%CV)	3.7		2.9		3.7			3.2		
* Inter day Accuracy (%Actual)	100		102		99.7			96.4		

Note: * = Results are reported as inter run

Bioequivalence Study No.BA18647469 Valsartan										
Parameter	Standard Curve Samples									
Concentration (µg/mL)	0.02000	0.04000	0.08000	0.2000	0.6000	1.200	2.400	4.800	9.600	12.00

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* Inter day Precision (%CV)	1.9	3.0	3.7	2.1	2.0	2.0	2.4	2.2	2.2	2.1
* Inter day Accuracy (%Actual)	98.5	101	102	104	102	102	99.7	98.6	97.0	95.3
Linearity (r ² value)	0.9963320 – 0.9996418									
Linearity Range (µg/mL)	0.02000 – 12.00									
Sensitivity/ LOQ (µg/mL)	0.02000									
Bioequivalence Study No.BA18647469 Valsartan										
Parameter	Quality Control Samples									
Concentration (µg/mL)	LQC 0.06000		MQC-2 0.7200		MQC-1 4.200			HQC 9.000		
* Inter day Precision (%CV)	3.6		2.8		3.6			3.2		
* Inter day Accuracy (%Actual)	98.5		100		97.9			95.3		

Note: * = Results are reported as inter run

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	☒ Yes, for both analytes ☐ No Highest C _{max} observed: SAC: 5.748 µg/mL VAL: 9.568 µg/mL
Are there any concerns related to sample analysis (including rejected runs, reinjection, sample dilution, etc.)? If yes, comment below or consult TL/tertiary reviewer for additional actions	☐ Yes ☒ No, for both analytes
Were 20% of chromatograms included?	☒ Yes, for both analytes ☐ No (52 x 20% = 10.4 ~ 11) The applicant provided chromatograms for 12 subjects ☐ - for both analytes)
Were chromatograms serially or randomly selected?	☒ serially, for both analytes ☐ randomly
Any interfering peaks in chromatogram?	☐ Yes ☒ No, for both analytes
Were the chromatograms submitted by the firm acceptable?	☒ Yes, for both analytes ☐ No
Were 100% raw analytical data, including failed runs, provided?	☒ Yes, for both analytes ☐ No

4.1.1.3.3 Reanalysis of Study Samples

Sacubitril Study No. BA18647469 Additional information in Module 5/Section 5.3.1.4/ Sample Analysis Report/ Page 59 to 65 of 135								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0.00	0.00	0	0	0.00	0.00
Auto injector vial leaked	0	1	0.00	0.04	0	1	0.00	0.04
High internal standard	0	1	0.00	0.04	0	1	0.00	0.04
Instrument malfunction	6	12	0.56	0.53	6	12	0.56	0.53
Total	6	14	0.56	0.61	6	14	0.56	0.61

Note: Total number of samples assayed = 3336

Total number of samples assayed for Test Product (T) = 1080

Total number of samples assayed for Reference Product (R) = 2256

Valsartan Study No. BA18647469 Additional information in Module 5/Section 5.3.1.4/ Sample Analysis Report/ Page 59 to 65 of 135								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0.00	0.00	0	0	0.00	0.00
Auto injector vial leaked	0	1	0.00	0.04	0	1	0.00	0.04
High internal standard	0	1	0.00	0.04	0	1	0.00	0.04
Instrument malfunction	6	12	0.56	0.53	6	12	0.56	0.53
Poor Chromatography	1	0	0.09	0.00	1	0	0.09	0.00
Total	7	14	0.65	0.61	7	14	0.65	0.61

Does the reviewer agree with the reanalysis of study samples: analytical and/or PK repeat?	☒ Yes, for both analytes ☐ No
If no, is recalculation of PK parameters necessary?	☐ Yes ☐ No ☒ N/A

Did recalculation of PK parameters change the study outcome?	☐ Yes ☐ No ☒ N/A
Are the PK parameters of reanalysis still within the acceptance limits for the 90% CI?	☐ Yes ☐ No ☒ N/A

Comments on Bioanalytical Results: Adequate

1. Accepted and Rejected Runs:

The applicant reported a total of 38 accepted, 1 reinjected, and zero rejected analytical runs for both analytes for the fasting study.

2. Reanalysis of Study Samples:

SAC: One (01) sample each was reassayed under codes Auto injector vial leaked (AIVL) and High internal standard (ISTD), and eighteen (18) samples were reassayed under code Instrument malfunction (IMF). Per assessor verification of the numerical summary (raw) data for SAC, the identification, repeat and reporting of these twenty (20) sample concentrations is appropriate per the repeat analysis standard operating procedure (SOP), [REDACTED]. Therefore, repeats for SAC for the fasting study are acceptable.

VAL:

One (01) sample each was reassayed under codes AIVL, High ISTD and Poor Chromatography (PC) as well as eighteen (18) samples were reassayed under code IMF. Per assessor verification of the numerical summary (raw) data for VAL, the identification, repeat and reporting of these twenty-one (21) sample concentrations is appropriate per the repeat analysis SOP. Therefore, repeats for VAL for the fasting study are acceptable.

3. Incurred Sample Reanalysis (ISR):

The assessor verified that the applicant performed ISR on 278 samples (for both analytes) out of 3336 analyzed samples in accordance with FDA's bioanalytical method validation (BAMV) guidance (May 2018). The concentrations from 100% (for both analytes) of the ISR samples were found to be within $\pm 20\%$ deviation from nominal concentration. The applicant's ISR results met both the applicant's own criteria per ISR SOP, [REDACTED] and FDA's BAMV guidance (May 2018).

4. Re-injections/Batch resubmissions:

A total of one (01) batch run (run # ISR 02) was resubmitted in its entirety due to stoppage of the original run owing to instrument malfunction error. The assessor verified that this is in accordance with the applicant's Sample Analysis SOP, [REDACTED]. Further, from numerical summary (raw) data, the assessor verified that the run # [REDACTED] was stopped at sample ID [REDACTED] for both analytes and that the duration of samples in autosampler (acquisition date/time difference between the first sample of the original ISR run to the last sample from reinjected run) is 19.0097 hours which is covered by the validated autosampler stability of 124 hours (at 15°C

to 30°C) and 123 hours (at 2°C to 10°C) for both analytes. Therefore, the assessor considers the batch reinjection acceptable.

4.1.1.4 Pharmacokinetic Results

Assessor Note: Per the current DBI policy, for pivotal study BE analyses based on replicate study design (i.e. partial replicate in the case of the current ANDA), the final dataset should include all available data (i.e. all analyzed samples) for all subjects, including those for the subjects who were excluded from the statistical analyses per the applicant's study protocol. The applicant provided fasting study datasets for both analytes did not include the analyzed sample data for dropouts, subjects (S) [redacted]. Accordingly, the applicant will be asked to provide revised concentration and PK datasets after including the data for these subjects as well as the PK and statistical analysis results from the updated datasets. Therefore, the currently provided fasting study datasets for both analytes are incomplete and the assessor's statistical analysis for both analytes for the fasting study will be conducted in the next assessment following the applicant's satisfactory response to the above-mentioned deficiency.

4.1.1.4.1 Arithmetic Mean Pharmacokinetic Parameters (All Periods) – Applicant Calculated

SAC:

PARAMETER	Test Product: Sacubitril and Valsartan Tablets 97 /103 mg		Reference Product: ENTRESTO TM (Sacubitril/Valsartan) Tablets 97 mg/103 mg	
	N	Arithmetic mean ±Std Deviation (Coeff of Variation (%))	N	Arithmetic mean ±Std Deviation (Coeff of Variation (%))
Cmax (µg/mL)	45	2.161 ± 1.162 (53.754)	90	2.040 ± 0.824 (40.412)
AUCt (hr*µg/mL)	45	2.603 ± 0.708 (27.193)	90	2.429 ± 0.718 (29.569)
AUCi (hr*µg/mL)	45	2.636 ± 0.702 (26.633)	88^	2.487 ± 0.675 (27.139)
AUC_%Extrap_obs	45	1.410 ± 1.776 (125.982)	88	1.131 ± 1.113 (98.353)
Kel (1/hr)	45	0.872 ± 0.255 (29.268)	88^	0.886 ± 0.247 (27.839)
tHalf (hr)	45	0.890 ± 0.379 (42.559)	88^	0.854 ± 0.287 (33.594)
Tmax (hr)#	45	0.500 (0.333 - 5.000)	90	0.500 (0.333 - 5.000)

Notes:

Tmax is presented as Median (Range)

^ For Reference Product, Subject [redacted] (Period-I) and Subject [redacted] (Period-III) did not exhibited a terminal log-linear phase in the concentration versus time profile, so AUCi, AUC_%Extrap_obs, Kel & tHalf

parameters were not estimated. Hence, N=88 instead of 90 for AUCi, AUC_%Extrap_obs, Kel & tHalf parameters.

VAL:

PARAMETER	Test Product: Sacubitril and Valsartan Tablets 97/103 mg		Reference Product: ENTRESTO™ (Sacubitril/Valsartan) Tablets 97 mg/103 mg	
	N	Arithmetic mean ±Std Deviation (Coeff of Variation (%))	N	Arithmetic mean ±Std Deviation (Coeff of Variation (%))
Cmax (µg/mL)	45	4.563 ± 1.867 (40.920)	90	4.885 ± 1.594 (32.633)
AUCt (hr*µg/mL)	45	28.802 ± 12.031 (41.772)	90	30.334 ± 10.692 (35.249)
AUCi (hr*µg/mL)	45	29.167 ± 12.079 (41.414)	90	30.702 ± 10.737 (34.972)
AUC_%Extrap_obs	45	1.552 ± 1.545 (99.517)	90	1.482 ± 1.675 (113.000)
Kel (1/hr)	45	0.112 ± 0.031 (27.677)	90	0.108 ± 0.028 (26.012)
tHalf (hr)	45	6.648 ± 1.895 (28.509)	90	6.777 ± 1.654 (24.412)
Tmax (hr) [#]	45	1.500 (1.000 - 3.500)	90	1.750 (1.000 - 4.000)

[#] Tmax is presented as Median (Range)

4.1.1.4.2 Arithmetic Mean Pharmacokinetic Parameters – Assessor Calculated

Assessor Note:

Not calculated at this time. Please see assessor note in section 4.1.1.4 for details.

4.1.1.4.3 Geometric Means and 90% Confidence Intervals - Applicant Calculated

SAC:

Sacubitril and Valsartan Tablets (No of subjects completed= 45) 1x 97 mg / 103 mg Least Square Geometric Means, Ratio of Means, and 90% Confidence Intervals Fasting Bioequivalence Study (BA18647469)						
Parameter	Test	N	RLD	N	Ratio	90% CI
AUCt (µg*hr/mL)	2.526	45	2.243	90	112.60%	NA
AUCi (µg*hr/mL)	2.558	45	2.414	88 [^]	105.99%	(102.77%;109.32%)
Cmax (µg /mL)	1.897	45	1.818	90	104.33%	NA

Notes:-

NA = Not Applicable; within subject standard deviation of reference product (S_{WR}) of Cmax and AUCt were greater than 0.294. Hence, Scaled Average Bioequivalence approach was used to assess bioequivalence for Cmax and AUCt.

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^ For Reference Product, Subject [] (Period-I) and Subject [] (Period-III) did not exhibit a terminal log-linear phase in the concentration versus time profile, so AUCi, AUC_%Extrap_obs, Kel & tHalf parameters were not estimated. Hence, N=88 instead of 90 for AUCi, AUC_%Extrap_obs, Kel & tHalf parameters.

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	Outcome
LAUCt	1.12^	NA	NA	0.3200	0.566	-0.1649	Scaled Average Bioequivalence	Bioequivalent
LAUCi	105.99%*	102.77%	109.32%	0.0049	0.070	NA	Average Bioequivalence	Bioequivalent
LCmax	1.04^	NA	NA	0.2998	0.548	-0.1683	Scaled Average Bioequivalence	Bioequivalent

Notes:- * T/R ratio presented in percentage (%) of Unscaled average bioequivalence method.

^point estimate of Scaled average bioequivalence method as per protocol.

NA = Not Applicable

VAL:

Sacubitril and Valsartan Tablets (No of subjects completed= 45) 1x 97 mg / 103 mg Least Square Geometric Means, Ratio of Means, and 90% Confidence Intervals Fasting Bioequivalence Study (BA18647469)						
Parameter	Test	N	RLD	N	Ratio	90% CI
AUCt (µg*hr/mL)	26.164	45	27.612	90	94.76%	NA
AUCi (µg*hr/mL)	26.575	45	28.031	90	94.81%	NA
Cmax (µg /mL)	4.130	45	4.505	90	91.67%	NA

Note:- NA = Not Applicable; The within subject standard deviation of reference product (S_{WR}) of Cmax, AUCt and AUCi were greater than 0.294. Hence, Scaled Average Bioequivalence approach was used to assess bioequivalence for Cmax, AUCt and AUCi.

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	Outcome
LAUCt	0.95	NA	NA	0.2217	0.471	-0.1190	Scaled Average Bioequivalence	Bioequivalent
LAUCi	0.95	NA	NA	0.2060	0.454	-0.1101	Scaled Average Bioequivalence	Bioequivalent
LCmax	0.92	NA	NA	0.2088	0.457	-0.1004	Scaled Average Bioequivalence	Bioequivalent

Note:- NA = Not Applicable

4.1.1.4.4 Geometric Means and 90% Confidence Intervals - Assessor Calculated

Assessor Note:

Not calculated at this time. Please see assessor note in section 4.1.1.4 for details.

4.1.1.4.5 Additional Information for the Study

Root Mean Square Error	AUCT, AUCI, Cmax:
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	<u>SAC and VAL</u> : Not available as assessor's SAS analysis is currently pending.
Is there a T_{max} difference between Test and Reference? If yes, please provide brief explanation (or detailed explanation, including T_{max} analysis, for substantial difference).	<u>SAC and VAL</u>: ☐ Yes ☐ No ☒ To Be Evaluated <u>Applicant Calculated</u>: <u>SAC</u>: Median T_{max} T/R = 0.500/0.500 = 1 Range: T and R (0.333- 5.000) <u>VAL</u>: Median T_{max} T/R = 1.500/1.750 = 0.86 Range: T (1.000- 3.500) and R (1.000- 4.000) <u>Assessor Calculated – SAC and VAL</u>: Not calculated at this time. Please see assessor note in section 4.1.1.4
Were the subjects dosed in groups? If yes, was the statistical analysis proper? Is reanalysis by reviewer necessary?	<u>SAC and VAL</u>: ☐ Yes ☒ No
Are there measurable drug concentrations at 0 hr? If yes, please comment (and take necessary action, if needed).	<u>SAC and VAL</u>: ☐ Yes ☒ No
Are there first measurable drug concentration as C_{max}? If yes, please comment.	<u>SAC and VAL</u>: ☐ Yes ☒ No
Are there C_{max} at the first time point? If yes, is the study (sample) design adequate?	<u>SAC and VAL</u>: ☐ Yes ☒ No

Assessor Note:

Assessor's evaluation of the AUC_{0-t}/AUC_∞ ratio and group analysis consideration for both analytes is not available as this time and will be presented following the assessor's statistical evaluation of BE (SAS run) for this pivotal study. Please see assessor note in section 4.1.1.4. for further details.

Comments on PK results: Inadequate

- As stated in the assessor note in section 4.1.1.4, the concentration datasets for both analytes for this pivotal study as currently provided by the applicant cannot be used to adequately conduct the assessor's BE determination for this study. Therefore, assessor's evaluation of PK results for the current study is currently incomplete and will be presented in the next assessment.

4.1.1.5 Overall Comment

Was the fasting bioequivalence study acceptable? Not acceptable (deficiency pertaining to SAS concentration dataset submission for both analytes).

Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study (Assessor Calculated)

Not calculated at this time. Please see assessor note in section 4.1.1.4 for details.

Mean Plasma Concentration Profile, Single-Dose Fasting Bioequivalence Study (Assessor Calculated)

Not calculated at this time. Please see assessor note in section 4.1.1.4 for details.

4.1.2 Single-Dose Fed Bioequivalence Study

4.1.2.1 Study Design

4.1.2.1.1 Study Information

Study Number	BA18647470
Study Title	Single dose oral bioequivalence study of Sacubitril and Valsartan Tablets 97 mg/103 mg and 'ENTRESTO™' (Sacubitril and Valsartan) Tablets 97 mg/103 mg in healthy adult human subjects under fed conditions.
Clinical Site (Name & Address)	Cliantha Research Limited Sigma-1 Corporate, B/H Rajpath Club, Opposite Mann Party Plot, Off. S.G. Highway, Bodakdev, Ahmedabad-380 054, Gujarat, India
Principal Clinical Investigator	Dr. Mayur Soni, MBBS msoni@cliantha.in & pi@cliantha.in
Dosing Dates	Period-I (P1): 3/26/2019 Period-II (P2): 4/1/2019 Period-III (P3): 4/7/2019
Analytical Site (Name & Address)	(b)(4)
Analysis Dates	04/11/2019 to 04/22/2019
Principal Analytical Investigator	(b)(4)
Sample Storage : (a) Duration (no. of days from the first day of sample collection to the last day of sample analysis) (b) Temperature Range (e.g., -20°C to -80°C)	(For Sacubitril and Valsartan) (a) 27 days (b) -20°C ± 10°C temperature
Long-Term Storage Stability (LTSS) Coverage (no. days @ temp °C)	(For Sacubitril and Valsartan) 273 days at -20°C ± 10°C temperature [For Sacubitril and Valsartan fortified with Metabolite Sacubitrilat (LBQ657) and 4-Hydroxy Valsartan (6.000/12.00 µg/mL)] 274 days at -20°C ± 10°C temperature LTSS study reports and data are presented in Module 5/ Section 5.3.1.4/ Attachment 6-3/ Addendum-II to the Method Validation Report/ Section 2.1/ Page 8 (For Sacubitril and Valsartan) LTSS study reports and data are presented in Module 5/ Section 5.3.1.4/ Attachment 6-3/ Addendum-II to the Method Validation Report/ Section 2.2/ Page 8

	[For Sacubitril and Valsartan fortified with Metabolite Sacubitril at (LBQ657) and 4-Hydroxy Valsartan (6.000/12.00 µg/mL)]
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4.1.2.1.2 Product (Bio-batch) Information

Note: The product information for fed study is the same as that for the fasting study (See section 4.1.1.1.2 for details).

4.1.2.1.3 Study Design, Single-Dose Fed Bioequivalence Study

Number of Subjects	Enrolled: 48 + 4 extra subjects [] Dosed: 48 (P1), 45 (P2), 45 (P3) Completed: 45 [] replaced with extra subject [] - extra subjects [] were not dosed; [] were discontinued) Samples Analyzed: 48 (45 completed and 03 discontinued subjects) Statistically Analyzed: 45
No. of Sequences	3
No. of Periods	3
No. of Treatments	2
No. of Groups	1
Washout Period	06 days
Randomization	☒ Yes ☐ No
Blood Sampling Times	Pre-dose (0.0 hour) and at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.333, 2.667, 3.0, 3.333, 3.667, 4.0, 4.5, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0, 36.0 and 48.0 hours post dose in each period.
IRB Approval	☒ Yes Date: [] ☐ No Date: 09/25/2018 (version 01) IRB approval predates period 01 dosing (03/26/2019).
Informed Consent	☒ Yes ☐ No Date: 09/25/2018 (version 01, English and Gujarati)
Length of Fasting	At least 10 hours prior to serving pre-dose standardized high-calorie & high-fat breakfast until at least 04 hours post-dose in each period.
Length of Confinement	At least 11 hours prior to dosing until at least 48 hours post dose in each period.
Was the drug product administered per labeling (for specialized dosage forms e.g. ODT)?	☐ Yes ☐ No ☒ N/A
Safety Monitoring	☒ Yes ☐ No

Standard FDA Meal Used?	☐ Yes ☒ No
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If No, then meal components and composition is listed in the table below						
Composition of Non-standard FDA Meal Used in Fed Bioequivalence Study						
Ingredients		Amount*	Energy	Protein	Fat	Carbohydrate
		(g)	(kcal)	(kcal)	(kcal)	(kcal)
Milk (Sterilised Flavoured)	Milk	250 mL	221.75	32	69.75	120
Chicken Dana	Chicken	70g	120.036	63.336	56.7	0
	Refined Flour	20g	69.072	8.288	1.368	59.416
	Oil	20 mL	180	0	180	0
Bread Butter	Bread	20g	49.02	6.24	1.26	41.52
	Butter	10g	72.2	0.2	72	0
Potato Chaat	Potato	40g	27.116	2.464	0.828	23.824
	Oil	5 mL	45	0	45	0
Paneer	Paneer	15g	38.713	11.316	19.953	7.444
	Oil	2 mL	18	0	18	0
Boiled Egg Masala	Egg	50g	84.78	26.28	58.5	0
TOTAL			925.687	150.124	523.359	252.204
PERCENTAGE			NA	16.218	56.537	27.245

Comments on Study Design: Adequate

1. As noted per assessor comment under section 4.1.1.1.3 of this assessment, the fed study sampling time points, as well as sampling and washout durations are appropriate with respect to both analytes. Additionally, the assessor verified that there are no instances of first time point C_{max} for either analyte.
2. Per FDA Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies (December 2002), *a high-fat (approximately 50 percent of total caloric content of the meal) and high-calorie (approximately 800-1000 calories) meal is recommended as a test meal for food-effect BA and fed BE studies. The test meal should derive approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively. The caloric breakdown of the test meal should be provided in the study report. If the caloric breakdown of the meal is significantly different from the one described above, the sponsor should provide a scientific rationale for this difference.* Based on the meal menu provided by the applicant, the total energy from the meal is 925.687 calories and the energy from protein, carbohydrates and fat is 150.124, 252.204, and 523.359 calories, respectively. Although the applicant used a modified high-fat high calorie breakfast in the fed bioequivalence study, the caloric breakdown of the test meal provided by the applicant is consistent with the Agency recommendation.

3. Per study protocol, subjects completing all periods (n=45) were included in BE evaluation with unscaled average BE (ABE) or reference scaled average bioequivalence (RSABE) method depending on the observed S_{WR} for each primary PK parameter. Per applicant, of the subjects to be included in the PK and statistical analysis per protocol, the subjects who completed two periods with reference treatment (n=45) and completed the study were included to estimate the S_{WR} . For both analytes, since S_{WR} was < 0.294 for C_{max} , AUCT, and AUCI, BE for both analytes was concluded using ABE approach. The study design and statistical analysis approach are acceptable.

4.1.2.2 Clinical Results

4.1.2.2.1 Demographic Profile of Subjects

Study No. BA18647470			
		Treatment Groups	
		Test Product (T) N = 45	Reference Product (R) N = 45
Age (years)	Mean $\pm$ SD	32 ($\pm$ 7)	32 ($\pm$ 7)
	Range	18 - 44	18 - 44
Age Groups	< 18	00 (0%)	00 (0%)
	18 – 40	38 (84.44%)	38 (84.44%)
	41 – 64	07 (15.56%)	07 (15.56%)
	65 – 75	00 (0%)	00 (0%)
	> 75	00 (0%)	00 (0%)
Sex	Male	45 (100%)	45 (100%)
	Female	00 (0%)	00 (0%)
Race	Asian	45 (100%)	45 (100%)
	Black	00 (0%)	00 (0%)
	Caucasian	00 (0%)	00 (0%)
	Hispanic	00 (0%)	00 (0%)
	Other	00 (0%)	00 (0%)
BMI (Kg/m ²)	Mean $\pm$ SD	23.4 ($\pm$ 3.5)	23.4 ($\pm$ 3.5)
	Range	18.7 – 29.8	18.7 – 29.8

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Tobacco users/Smokers	Yes	00 (0%)	00 (0%)
	No	45 (100%)	45 (100%)

Is the demographics profile of subjects completing the bioequivalence study in agreement with the current drug product recommendation?	☒ Yes ☐ No
--	---

4.1.2.2.2 Dropout Information

Study No. BA18647470				
Subject No	Reason for dropout/replacement	Period	Replaced?	Replaced with
(b)(6)	Reason: Withdrawal by subject Date: Time: 0704 hrs.	NA	Yes	(b)(6)
	Reason: Protocol violation (Subject found alcohol positive in alcohol breath test during period II check in.) Date: Time: 1149 hrs. Last Treatment Received: Reference	Period I	No	NA
	Reason: Withdrawal by subject Date: Time: 2310 hrs. Last Treatment Received: Reference	Period I	No	NA
	Reason: Protocol violation (Subject found THC positive in urine drug of abuse test during period II check in.) Date: Time: 1757 hrs. Last Treatment Received: Test	Period I	No	NA

NA: Not applicable

Are dropouts appropriate? If no, please comment.	☒ Yes, the reviewer verified this information from the Case Report Forms (CRFs) ☐ No
--	---

4.1.2.2.3 Study Adverse Events

There were no adverse events reported during conduct of the study.

Body System / Adverse Event	Reported Incidence by Treatment Groups
	Fed Bioequivalence Study Study No. BA18647470

	Test (T)	Reference (R)
NONE		

Were subjects who experienced vomiting included in statistical analysis?	☐ Yes ☐ No ☒ N/A
If yes, does the time of emesis exceed two times the median Tmax value (immediate release products) or the labeled dosing interval (modified release products)? Please comment.	☐ Yes ☐ No ☒ N/A
Was the adverse event profile observed comparable for the test and reference product?	☒ Yes ☐ No
Are there any serious adverse events or death?	☐ Yes ☒ No
If yes, then if the study conducted in US, are they reported to the OGD Safety Committee?	☐ Yes ☐ No ☒ N/A
Are there any other safety concerns based on the adverse event profile?	☐ Yes ☒ No

4.1.2.2.4 Protocol Deviations

Study No. BA18647470		
Type	Subject #s (Test) (T)	Subject #s (Reference) (R)
Blood draw time point deviations, Period I	(b)(6)	
Blood draw time point deviations, Period II		
Blood draw time point deviations, Period III		

Note: Superscript above the subject number indicates the number of multiple occurrences of the indicated deviation recorded by that subject.

If the firm used nominal time points, the sampling time deviations (if any) > 5% and 90% CI of any PK parameters is border line, please reanalyze data using actual sampling time.	☒ Actual ☐ Nominal
Is the dropout/withdrawal/exclusion of subjects and protocol deviations as per the criteria mentioned in the IRB approved study protocol?	☒ Yes ☐ No

Comments on Clinical Results: Adequate

1. Post-dose sampling time deviations are not likely to affect study outcome since actual sampling time points are used in the dataset used for BE determination.
2. There was no adverse event reported and hence no medication was administered concomitantly during the study.

4.1.2.3 Bioanalytical Results

4.1.2.3.1 SOPs dealing with Sample Analysis including Repeat Analysis

Note: The SOPs for fed study are the same as and already listed under the fasting study section (See assessment section 4.1.1.3.1 for details).

4.1.2.3.2 Sample Analysis Calibration and Quality Control

Bioequivalence Study No.BA18647470 Sacubitril										
Parameter	Standard Curve Samples									
Concentration (µg/mL)	0.01000	0.02000	0.04000	0.1000	0.3000	0.6000	1.200	2.400	4.800	6.000
* Inter day Precision (%CV)	1.0	1.9	2.5	2.4	1.7	2.4	1.8	1.5	2.3	3.4
* Inter day Accuracy (%Actual)	99.9	101	98.3	101	102	103	99.2	98.5	98.5	99.7
Linearity (r ² value)	0.9952042 – 0.9998444									
Linearity Range (µg/mL)	0.01000 – 6.000									
Sensitivity/LOQ (µg/mL)	0.01000									
Bioequivalence Study No.BA18647470 Sacubitril										
Parameter	Quality Control Samples									
Concentration (µg/mL)	LQC 0.03000		MQC-2 0.3600		MQC 1.400		MQC-1 2.100		HQC 4.500	
* Inter day Precision (%CV)	3.7		3.9		2.5		3.2		3.3	
* Inter day Accuracy (%Actual)	96.2		101		96.9		95.0		92.8	

Note: * = Results are reported as inter run

Additional quality control sample (MQC-1.400 µg/mL) was added from Run 10

Assessor's Note: Per the MVR for SAC, all QCs per table above with the exception of MQC- 1.400 µg/mL were validated. However, since the MQC falls within the overall validated QC range and the within study precision and accuracy (P&A) is acceptable, the non-validation of the MQC is not expected to be a concern.

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Single-Dose Fed Bioequivalence Study Review

Bioequivalence Study No.BA18647470 Valsartan										
Parameter	Standard Curve Samples									
Concentration (µg/mL)	0.02000	0.04000	0.08000	0.2000	0.6000	1.200	2.400	4.800	9.600	12.00
* Inter day Precision (%CV)	1.9	3.4	2.5	2.1	2.2	2.0	2.8	2.3	2.6	3.2
* Inter day Accuracy (%Actual)	100	100	98.7	100	101	102	98.8	99.2	99.1	101
Linearity (r ² value)	0.9975335 – 0.9998462									
Linearity Range (µg/mL)	0.02000 – 12.00									
Sensitivity/LOQ (µg/mL)	0.02000									
Bioequivalence Study No.BA18647470 Valsartan										
Parameter	Quality Control Samples									
Concentration (µg/mL)	LQC 0.06000		MQC-2 0.7200		MQC 2.800		MQC-1 4.200		HQC 9.000	
* Inter day Precision (%CV)	3.9		4.2		2.5		2.9		3.4	
* Inter day Accuracy (%Actual)	96.5		101		97.6		95.3		93.5	

Note: * = Results are reported as inter run

Additional quality control sample (MQC-2.800 µg/mL) was added from Run 10

Assessor's Note: Per the MVR for SAC, all QCs per table above with the exception of MQC- 2.800 µg/mL were validated. However, since the MQC falls within the overall validated QC range and the within study precision and accuracy (P&A) is acceptable, the non-validation of the MQC is not expected to be a concern.

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	☒ Yes, for both analytes ☐ No Highest C _{max} observed: SAC: 3.800 µg/mL VAL: 4.949 µg/mL
Are there any concerns related to sample analysis (including rejected runs, reinjection, sample dilution, etc.)? If yes, comment below or consult TL/tertiary reviewer for additional actions	☐ Yes ☒ No, for both analytes
Were 20% of chromatograms included?	☒ Yes, for both analytes ☐ No (52 x 20% = 10.4 ~ 11)

	The applicant provided chromatograms for 14 subjects (-- for both analytes)
Were chromatograms serially or randomly selected?	☒ serially, for both analytes ☐ randomly
Any interfering peaks in chromatogram?	☐ Yes ☒ No, for both analytes
Were the chromatograms submitted by the firm acceptable?	☒ Yes, for both analytes ☐ No
Were 100% raw analytical data, including failed runs, provided?	☒ Yes, for both analytes ☐ No

4.1.2.3.3 Reanalysis of Study Samples

Sacubitril Study No. BA18647470 Additional information in Module 5/Section 5.3.1.4/ Sample Analysis Report/ Page 62 of 126								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0.00	0.00	0	0	0.00	0.00
Low internal standard	0	1	0.00	0.04	0	1	0.00	0.04
Total	0	1	0.00	0.04	0	1	0.00	0.04

Note: Total number of samples assayed = 3450

Total number of samples assayed for Test Product (T) = 1150

Total number of samples assayed for Reference Product (R) = 2300

Valsartan Study No. BA18647470 Additional information in Module 5/Section 5.3.1.4/ Sample Analysis Report/ Page 62 of 126								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0.00	0.00	0	0	0.00	0.00
Low internal standard	0	1	0.00	0.04	0	1	0.00	0.04
Total	0	1	0.00	0.04	0	1	0.00	0.04

Note: Total number of samples assayed = 3450

Total number of samples assayed for Test Product (T) = 1150

Total number of samples assayed for Reference Product (R) = 2300

Does the reviewer agree with the reanalysis of study samples: analytical and/or PK repeat?	☒ Yes ☐ No
If no, is recalculation of PK parameters necessary?	☐ Yes ☐ No ☒ N/A
Did recalculation of PK parameters change the study outcome?	☐ Yes ☐ No ☒ N/A
Are the PK parameters of reanalysis still within the acceptance limits for the 90% CI?	☐ Yes ☐ No ☒ N/A

Comments on Bioanalytical Results: Adequate

1. Accepted and Rejected Runs:

The applicant reported a total of 36 accepted, 3 reinjected, and zero rejected analytical runs for both analytes for the fed study.

2. Reanalysis of Study Samples:

SAC and VAL: One (01) sample for each analyte was reassayed under code Low IS. Per assessor verification of the numerical summary (raw) data for SAC and VAL, the identification, repeat and reporting of these sample concentrations is appropriate per the repeat analysis SOP. Therefore, these fed study repeats are acceptable.

3. Incurred Sample Reanalysis (ISR):

The assessor verified that the applicant performed ISR on 278 (SAC) and 276 (VAL) samples out of 3450 analyzed samples in accordance with FDA's bioanalytical method validation (BAMV) guidance (May 2018). The concentrations from 99.6% (SAC) and 100% (VAL) of the samples selected for ISR were found to be within $\pm 20\%$ deviation from nominal concentration. The applicant's ISR results met both the applicant's own criteria per ISR SOP and FDA's BAMV guidance (May 2018).

4. Re-injections/Batch resubmissions:

A total of three (03) batch runs (Prestudy, Run 01 [reinjected twice], and Run 02) were resubmitted in their entirety due to stoppage of the original runs as a result of software or instrument (hardware) malfunction (i.e. capillary flow error, detector saturation error). The assessor verified that these batch reinjections are in accordance with the applicant's Sample Analysis SOP and applicant provided explanation for the batch reinjections was verified based on the provided numerical summary (raw) data for both analytes. It is further verified that the durations of the samples from the reinjected batches in the autosampler are 17.089 hours (Prestudy), 48.0 hours (Run 01) and 25.873 hours (Run 02), respectively, which are all covered by the validated autosampler stability of 124 hours (at 15°C to 30°C) and 123 hours (at 2°C to 10°C) for both analytes. Therefore, the assessor considers these batch reinjections acceptable.

4.1.2.4 Pharmacokinetic Results

Assessor Note: On similar lines as the assessor note under section 4.1.1.4 (fasting study), the applicant provided fed study datasets for both analytes did not include the analyzed sample data for dropouts, (b)(6). Accordingly, the applicant will be asked to provide revised concentration and PK datasets after including the data for these subjects as well as the PK and statistical analysis results from the updated datasets. Therefore, the currently provided fed study datasets for both analytes are incomplete and the assessor's statistical analysis for both analytes for the fed study will be conducted in the next assessment following the applicant's satisfactory response to the above-mentioned deficiency.

4.1.2.4.1 Arithmetic Mean Pharmacokinetic Parameters – Applicant Calculated

SAC:

PARAMETER	Test Product: Sacubitril and Valsartan Tablets 97 /103 mg		Reference Product: ENTRESTO™ (Sacubitril /Valsartan) Tablets 97 mg/103 mg	
	N	Arithmetic mean ±Std Deviation (Coeff of Variation (%))	N	Arithmetic mean ±Std Deviation (Coeff of Variation (%))
Cmax (µg/mL)	45	1.265 ±0.524 (41.395)	90	1.231 ±0.539 (43.818)
AUCt (hr*µg/mL)	45	2.022 ±0.357 (17.644)	90	1.987 ±0.380 (19.141)
AUCi (hr*µg/mL)	45	2.045 ±0.358 (17.531)	88^	2.008 ±0.379 (18.887)
AUC_%Extrap_obs	45	1.119 ±0.472 (42.172)	88^	1.207 ±0.758 (62.766)
Kel (1/hr)	45	0.870 ±0.215 (24.724)	88^	0.954 ±0.253 (26.535)
tHalf (hr)	45	0.852 ±0.245 (28.724)	88^	0.798 ±0.315 (39.409)
Tmax (hr)#	45	1.750 (0.500 - 4.500)	90	1.775 (0.500 - 5.000)

Note: # Tmax is presented as Median (Range)

^ For Reference Product, Subject- (Period-I) and Subject- (Period-II) did not exhibited a terminal log-linear phase in the concentration versus time profile, so AUCi, AUC_%Extrap_obs, Kel & tHalf parameters were not estimated. Hence, N=88 instead of 90 for AUCi, AUC_%Extrap_obs, Kel & tHalf parameters.

VAL:

PARAMETER	Test Product: Sacubitril and Valsartan Tablets 97 /103 mg		Reference Product: ENTRESTO™ (Sacubitril /Valsartan) Tablets 97 mg/103 mg	
	N	Arithmetic mean ±Std Deviation (Coeff of Variation (%))	N	Arithmetic mean ±Std Deviation (Coeff of Variation (%))
Cmax (µg/mL)	45	2.702 ±0.828 (30.641)	90	2.824 ±0.823 (29.150)

AUCt (hr*µg/mL)	45	17.419 ±5.754 (33.036)	90	17.320 ±5.535 (31.959)
AUCi (hr*µg/mL)	45	17.785 ±5.814 (32.689)	90	17.672 ±5.576 (31.551)
AUC_%Extrap_obs	45	2.159 ±0.892 (41.302)	90	2.107 ±0.829 (39.360)
Kel (1/hr)	45	0.106 ±0.032 (30.415)	90	0.112 ±0.033 (29.137)
tHalf (hr)	45	7.224 ±2.580 (35.722)	90	6.777 ±2.180 (32.169)
Tmax (hr)#	45	3.000 (1.250 - 5.000)	90	3.667 (1.250 - 5.000)

Note: #Tmax is presented as Median (Range)

4.1.2.4.2 Arithmetic Mean Pharmacokinetic Parameters – Assessor Calculated

Assessor Note:

Not calculated at this time. Please see assessor note in section 4.1.2.4 for details.

4.1.2.4.3 Geometric Means and 90% Confidence Intervals - Applicant Calculated

SAC:

Sacubitril and Valsartan Tablets (No of subjects completed= 45) 1x 97 mg / 103 mg Least Square Geometric Means, Ratio of Means, and 90% Confidence Intervals Fed Bioequivalence Study (BA18647470)						
Parameter	Test	N	RLD	N	Ratio	90% CI
AUCt (µg*hr/mL)	1.989	45	1.948	90	102.06%	(99.76%;104.42%)
AUCi (µg*hr/mL)	2.011	45	1.973	88^	101.94%	(99.67%;104.26%)
Cmax (µg /mL)	1.163	45	1.129	90	103.03%	(95.20%;111.50%)

Notes: -

The within subject standard deviation of reference product (S_{WR}) of Cmax, AUCt and AUCi were less than 0.294. Hence, Average Bioequivalence approach was used to assess bioequivalence for Cmax, AUCt and AUCi parameters.

^ For Reference Product, Subject [] (Period-I) and Subject [] (Period-II) did not exhibit a terminal log-linear phase in the concentration versus time profile, so AUCi, AUC_%Extrap_obs, Kel & tHalf parameters were not estimated. Hence, N=88 instead of 90 for AUCi, AUC_%Extrap_obs, Kel & tHalf parameters.

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	Outcome
LAUCt	102.06%	99.76%	104.42%	0.0038	0.062	NA	Average Bioequivalence	Bioequivalent
LAUCi	101.94%	99.67%	104.26%	0.0039	0.063	NA	Average Bioequivalence	Bioequivalent
LCmax	103.03%	95.20%	111.50%	0.0765	0.277	NA	Average Bioequivalence	Bioequivalent

Note:- NA = Not Applicable

VAL:

Sacubitril and Valsartan Tablets (No of subjects completed= 45) 1x 97 mg / 103 mg Least Square Geometric Means, Ratio of Means, and 90% Confidence Intervals Fed Bioequivalence Study (BA18647470)						
Parameter	Test	N	RLD	N	Ratio	90% CI
AUC _t (µg*hr/mL)	16.597	45	16.532	90	100.39%	(94.84%;106.27%)
AUC _i (µg*hr/mL)	16.964	45	16.888	90	100.46%	(95.01%;106.22%)
C _{max} (µg /mL)	2.591	45	2.707	90	95.72%	(90.11%;101.67%)

Note: -

The within subject standard deviation of reference product (S_{WR}) of C_{max}, AUC_t and AUC_i were less than 0.294. Hence, Average Bioequivalence approach was used to assess bioequivalence for C_{max}, AUC_t and AUC_i parameters.

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s _{2wr}	s _{WR}	Criteria Bound	Method Used	Outcome
LAUC _t	100.39%	94.84%	106.27%	0.0197	0.140	NA	Average Bioequivalence	Bioequivalent
LAUC _i	100.46%	95.01%	106.22%	0.0190	0.138	NA	Average Bioequivalence	Bioequivalent
LC _{max}	95.72%	90.11%	101.67%	0.0244	0.156	NA	Average Bioequivalence	Bioequivalent

Note:- NA = Not Applicable

4.1.2.4.4 Geometric Means and 90% Confidence Intervals - Assessor Calculated

Assessor Note:

Not calculated at this time. Please see assessor note in section 4.1.2.4 for details.

4.1.2.4.5 Additional Information for the Study

Root Mean Square Error	AUC _t , AUC _i , C _{max} : <u>SAC and VAL</u> : Not available as assessor's SAS analysis is currently pending.
Is there a T_{max} difference between Test and Reference? If yes, please provide brief explanation (or detailed explanation, including T _{max} analysis, for substantial difference).	<u>SAC and VAL</u> : ☐ Yes ☐ No ☒ To Be Evaluated <u>Applicant Calculated</u> : <u>SAC</u> : Median T _{max} T/R = 1.750/1.775 = 0.99 Range: T (0.500- 4.500) and R (0.500- 5.000) <u>VAL</u> : Median T _{max} T/R = 3.000/3.667 = 0.82

	<i>Range: T and R (1.250- 5.000)</i> <u>Assessor Calculated – SAC and VAL:</u> Not calculated at this time. Please see assessor note in section 4.1.1.4
Were the subjects dosed in groups? If yes, was the statistical analysis proper? Is reanalysis by reviewer necessary?	<u>SAC and VAL:</u> ☐ Yes ☒ No
Are there measurable drug concentrations at 0 hr? If yes, please comment (and take necessary action, if needed).	<u>SAC and VAL:</u> ☐ Yes ☒ No
Are there first measurable drug concentration as Cmax? If yes, please comment.	<u>SAC and VAL:</u> ☐ Yes ☒ No
Are there Cmax at the first time point? If yes, is the study (sample) design adequate?	<u>SAC and VAL:</u> ☐ Yes ☒ No

Assessor Note:

Assessor's evaluation of the AUC_{0-t}/AUC_∞ ratio and group analysis consideration for both analytes is not available as this time and will be presented following the assessor's statistical evaluation of BE (SAS run) for this pivotal study. Please see assessor note in section 4.1.2.4. for further details.

Comments on PK results: Inadequate

- As stated in the assessor note in section 4.1.2.4, the concentration datasets for both analytes for this pivotal study as currently provided by the applicant cannot be used to adequately conduct the assessor's BE determination for this study. Therefore, assessor's evaluation of PK results for the current study is currently incomplete and will be presented in the next assessment.

4.1.2.5 Overall Comment

Was the fasting bioequivalence study acceptable? Not acceptable (deficiency pertaining to SAS concentration dataset submission for both analytes).

Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study (Assessor Calculated)

Not calculated at this time. Please see assessor note in section 4.1.1.4 for details.

Mean Plasma Concentration Profile, Single-Dose Fasting Bioequivalence Study (Assessor Calculated)

Not calculated at this time. Please see assessor note in section 4.1.1.4 for details.

4.2 Formulation Data

4.2.1 Test Formulation

Ingredient	Amount (mg) / Tablet			Amount (%) / Tablet		
	Sacubitril and Valsartan Tablets 24 mg/ 26 mg	Sacubitril and Valsartan Tablets 49 mg / 51 mg	Sacubitril and Valsartan Tablets 97 mg/ 103 mg	Sacubitril and Valsartan Tablets 24 mg/ 26 mg	Sacubitril and Valsartan Tablets 49 mg / 51 mg	Sacubitril and Valsartan Tablets 97 mg/ 103 mg
(b)(4)						
Sacubitril and Valsartan						
Microcrystalline Cellulose (b)(4) USP-NF						
Crospovidone (b)(4) USP-NF						
Croscarmellose Sodium (b)(4) USP-NF						
Colloidal Silicon Dioxide (b)(4) USP-NF						
Talc (b)(4) USP						
Magnesium Stearate (b)(4) USP-NF						
(b)(4)						

(b)(4)						
Total	103.000	206.000	412.000	100.00	100.00	100.00

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(b) (4)

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Inactive Ingredients	Location in Formulation	Function of Formulation Component	Per Test strength	mg/tablet (of applicable strength)	Maximum amount (mg)/MDD (x8 for 50 mg, x4 for 100 mg, x2 for 200 mg)	IIG per unit limit (mg)	IIG Reference Source	IIG Reference Product Dosage Form	Above/Below/At IIG Limit
Microcrystalline Cellulose								oral tablet	Below
Crospovidone								oral tablet	Below
Croscarmellose Sodium								oral tablet	Below
Colloidal Silicon Dioxide								oral tablet	Below
Talc								oral tablet	Below
Magnesium Stearate								oral tablet	Below
(b)(4)									

(b)(4)

Titanium Dioxide	03F500057, Opadry Yellow 03F520058, and Opadry Pink 03F540048)	97/103 (200mg)	2.969	5.938	MDI: 9.104 (RLD, N207620)	RLD	oral tablet	Below
Macrogl/PEG 4000		24/26 (50mg)	0.300	2.400	MDI: 4.576 (RLD, N207620)	RLD	oral tablet	Below
Red Iron Oxide		24/26 (50mg)	0.0135	0.108	4.08 (A202987)	FDA IIG Database	oral tablet	Below
Yellow Iron Oxide		49/51 (100mg)	0.120	0.480	11.5 (A202696)	FDA IIG Database	oral tablet	Below
Black Iron Oxide		24/26 (50mg)	0.012	0.096	0.86 (N205122)	FDA IIG Database	oral capsule	Below

* Based on the higher of the three MDIs based on 50 mg, 100 mg and 200 mg strengths of the proposed generic product.

4.2.3 Formulation Proportionality

Tablet Strength	Inactive Ingredient	Micro-crystalline Cellulose	Cros-povidone	Cros-carmellose Sodium	Colloidal Silicon Dioxide	Talc	Magnesium Stearate	Hydro-mellose	Titanium Dioxide	PEG 4000	Talc	Iron Oxide Yellow	Iron Oxide Red	Iron Oxide Black	Total Additive Effect
	Function	Diluent	Disintegrant	Disintegrant	Glidant	Anti-adherent	Lubricant	Film coating material							
97 mg/103 mg	Amount (mg)	120.640	12.000	22.000	9.000	8.000	12.000	7.200	2.969	1.200	0.600	0.000	0.030	0.001	
	% (w/w)*	29.28%	2.91%	5.34%	2.18%	1.94%	2.91%	1.75%	0.72%	0.29%	0.15%	0.00%	0.01%	0.00%	
49 mg/51 mg	Amount (mg)	60.320	6.000	11.000	4.500	4.000	6.000	3.600	1.379	0.600	0.300	0.120	0.001		
	% (w/w)*	29.28%	2.91%	5.34%	2.18%	1.94%	2.91%	1.75%	0.67%	0.29%	0.15%	0.06%	0.00%	0.00%	

	% Difference to Bio Strength	(b)(4)	
24 mg/26 mg	Amount (mg)		
	% (w/w)* % Difference to Bio Strength		

(b)(4)	
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Are all strengths of the test product proportionally similar per the BA/BE guidance criteria?	☐ Yes	☐ No	☒ N/A
Are the amounts of all inactive ingredients, based on Maximum Daily Dose (MDD), within IIG (per unit) limits?	☐ Yes	☒ No	

If no, are they all within IIG (per day) limits?	☒ Yes ☐ No ☐ N/A
If no, are additional data or Pharm/Tox consult necessary?	☐ Yes ☐ No ☒ N/A
Are all color additives and elemental iron within limits specified by CFR (if applicable) or less than 0.1 % of the total unit weight (w/w)?	☒ Yes ☐ No ☐ N/A
Are all strengths of the test formulation acceptable?	☒ Yes ☐ No ☐ NA

Comments on Formulation: Adequate

1. All inactive ingredients in the test product formulation of both strengths are within approved IIG per day limit for use at the MDD level in adults. The test formulation does not contain any excipients that may pose safety concerns when used in the renally impaired patient population.

Per the IIG-MDD Master Spreadsheet,

(b)(4)

(b)(4)

2. The lower (biowaiver) strengths of the test product (i.e. SAC/VAL 24 mg/26 mg or 50 mg, and SAC/VAL 49 mg/51 mg or 100 mg) are considered proportionally similar that of the bio- strength (i.e. SAC/VAL 97 mg/103 mg or 200 mg) with excipient total additive effect (difference with respect to the bio-strength) of 0.04% and 0.12% respectively.

17
18

(b)(4)

DELETED PAGES INFORMATION SHEET

IT IS NOT REASONABLE TO SEGREGATE MEANINGFUL PORTIONS OF THE RECORD FOR RELEASE.

INFORMATION HAS BEEN WITHHELD IN ITS ENTIRETY IN ACCORDANCE WITH THE FOLLOWING EXEMPTIONS(S):

(b) (4)

5 U.S.C. 552 (b) (4) - trade secrets and commercial or financial information obtained from a person and privileged or confidential.

4.3 Dissolution Testing

4.3.1 Dissolution Data

Summary of In Vitro Dissolution Studies:

24 mg /26 mg:

SAC:

Dissolution Conditions		Apparatus:		(b)(4)									
		Speed of Rotation:											
		Medium:											
		Volume:											
		Temperature:											
Firm's Proposed Specifications				(b)(4)									
Dissolution Testing Site (Name, Address)				MSN Laboratories Private Limited – Formulations Division, Unit-II Survey Nos. 1277 & 1319 to 1324, Nandigama (Village) and (Mandal),Ranga Reddy District Pin Code-509228, Telangana, India									
Study Ref No.	Testing Date	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)				Study Report Location			
						10	15	20	30		45		
DPR-18046-00	05.01.2019	Sacubitril Valsartan Tablets, 24 mg /26 mg Tablet Batch No: DT1812055 Mfg Date:Dec-2018	24 mg /26 mg Tablet	12	Mean	68	85	93	98	100	Module 2		
					Range	(b)(4)							
					%CV	16.2	9.1	6.0	3.5	3.2			
	09.02.2019	ENTRESTOS (Sacubitril Valsartan) Film coated Tablets Lot No: FX000277 Exp Date: Dec-2020	24 mg /26 mg Tablet	12	Mean	55	78	93	94	96			
					Range	(b)(4)							

		Distributed By: Novartis pharmaceutical Corporation, East Hanover, NJ-07936			%CV	9.2	7.4	4.1	3.1	2.9	
Dissolution Conditions		Apparatus:		(b)(4)							
		Speed of Rotation:									
		Medium:									
		Volume:									
		Temperature:									
Firm's Proposed Specifications											
MSN Laboratories Private Limited – Formulations Division, Unit-II Survey Nos. 1277 & 1319 to 1324, Nandigama (Village) and (Mandal), Ranga Reddy District Pin Code-509228, Telangana, India											
Study Ref No.	Testing Date	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)				Study Report Location	
	04.01.2019	Sacubitril Valsartan Tablets, 24 mg /26 mg Batch No: DTI812056 Mfg Date:Dec-2018	24 mg /26 mg Tablet	12	Mean	66	82	89	95	98	Module 2
				Range	(b)(4)						
				%CV	12.7	10.2	8.5	6.5	4.6		
DPR-18046-00	09.02.2019	ENTRESTO (Sacubitril Valsartan) Film coated Tablets Lot No: FX000277 Exp Date: Dec-2020 Distributed By: Novartis pharmaceutical Corporation, East Hanover, NJ-07936	24 mg /26 mg Tablet	12	Mean	55	78	93	94	96	
				Range	(b)(4)						
				%CV	9.2	7.4	4.1	3.1	2.9		

Dissolution Conditions		Apparatus:		(b)(4)							
		Speed of Rotation:									
		Medium:									

		Volume:		(b)(4)						
		Temperature:								
Firm's Proposed Specifications										
Dissolution Testing Site (Name, Address)										
MSN Laboratories Private Limited – Formulations Division, Unit-II Survey Nos. 1277 & 1319 to 1324, Nandigama (Village) and (Mandal), Ranga Reddy District Pin Code-509228, Telangana, India										
Study Ref No.	Testing Date	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes)				Study Report Location	
					10	15	20	30		45
DPR-18046-00	07.01.2019	Sacubitril Valsartan Tablets, 24 mg /26 mg Batch No: DT1812057 Mfg Date: Dec-2018	24 mg /26 mg Tablet	12	Mean	73	90	97	101	103
					Range	(b)(4)				
	09.02.2019	ENTRESTO (Sacubitril Valsartan) Film coated Tablets Lot No: FX000277 Exp Date: Dec-2020 Distributed By: Novartis pharmaceutical Corporation, East Hanover, NJ-07936	24 mg /26 mg Tablet	12	%CV	19.8	11.2	6.6	3.8	2.9
					Mean	55	78	93	94	96
					Range	(b)(4)				
					%CV	9.2	7.4	4.1	3.1	2.9
Module 2										

VAL:

Dissolution Conditions		Apparatus:		(b)(4)						
		Speed of Rotation:								
		Medium:								
		Volume:								
		Temperature:								
Firm's Proposed Specifications				(b)(4)						
Dissolution Testing Site (Name, Address)		MSN Laboratories Private Limited – Formulations Division, Unit-II Survey Nos. 1277 & 1319 to 1324, Nandigama (Village) and (Mandal), Ranga Reddy District Pin Code-509228, Telangana, India								
Study Ref No.	Testing Date	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes)				Study Report Location	
DPR-18046-00	05.01.2019	Sacubitril Valsartan Tablets, 24 mg /26 mg Batch No: DT1812055 Mfg Date:Dec-2018	24 mg /26 mg Tablet	12	Mean	66	82	90	94	96
					Range	(b)(4)				
	09.02.2019	ENTRESTO (Sacubitril Valsartan) Film coated Tablets Lot No: FX000277 Exp Date: Dec-2020 Distributed By: Novartis pharmaceutical Corporation, East Hanover, NJ-07936	24 mg /26 mg Tablet	12	%CV	16.5	9.5	6.1	3.3	2.7
					Mean	55	78	91	93	94
					Range	(b)(4)				
Dissolution Conditions		Apparatus:		(b)(4)						
		Speed of Rotation:								
		Medium:								
		Volume:								
		Temperature:								

Firm's Proposed Specifications										
Dissolution Testing Site (Name, Address)		MSN Laboratories Private Limited – Formulations Division, Unit-II Survey Nos. 1277 & 1319 to 1324, Nandigama (Village) and (Mandal), Ranga Reddy District Pin Code-509228, Telangana, India								
Study Ref No.	Testing Date	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes)				Study Report Location	
					10	15	20	30		45
DPR-18046-00	04.01.2019	Sacubitril Valsartan Tablets, 24 mg /26 mg Batch No: DT1812056 Mfg Date: Dec-2018	24 mg /26 mg Tablet	12	Mean	66	80	87	92	95
					Range	(b)(4)				
	09.02.2019	ENTRESTO (Sacubitril Valsartan) Film coated Tablets Lot No: FX000277 Exp Date: Dec-2020 Distributed By: Novartis pharmaceutical Corporation, East Hanover, NJ-07936	24 mg /26 mg Tablet	12	%CV	12.2	9.7	8.2	6.2	4.2
					Mean	55	78	91	93	94
					Range	(b)(4)				
Dissolution Conditions		Apparatus:	(b)(4)							
										Speed of Rotation:
										Medium:
										Volume:
										Temperature:
Firm's Proposed Specifications										
Dissolution Testing Site (Name, Address)		MSN Laboratories Private Limited – Formulations Division, Unit-II Survey Nos. 1277 & 1319 to 1324, Nandigama (Village) and (Mandal), Ranga Reddy District Pin Code-509228, Telangana, India								
Study Ref No.	Testing Date	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes)				Study Report Location	
					10	15	20	30		45

DPR-18046-00	07.01.2019	Sacubitril Valsartan Tablets, 24 mg /26 mg Batch No: DT1812057 Mfg Date: Dec-2018	24 mg /26 mg Tablet	12	Mean	71	87	93	97	99	
					Range	(b)(4)					
					%CV	19.0	10.6	6.2	3.4	2.4	
					Mean	55	78	91	93	94	
					Range	(b)(4)					
	09.02.2019	ENTRESTO (Sacubitril Valsartan) Film coated Tablets Lot No: FX000277 Exp Date: Dec-2020 Distributed By: Novartis pharmaceutical Corporation, East Hanover, NJ-07936	24 mg /26 mg Tablet	12	%CV	8.7	7.1	3.8	2.8	2.5	

Module 2

49 mg /51 mg:

SAC:

Dissolution Conditions		Apparatus:		(b)(4)																	
		Speed of Rotation:																			
		Medium:																			
		Volume:																			
		Temperature:																			
Firm's Proposed Specifications				b)(4)																	
Dissolution Testing Site (Name, Address)		Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)		Dosage Strength & Form		No. of Dosage Units		Collection Times (minutes)				Study Report Location									
								Testing Date		10				15		20		30		45	
DPR-18046-00	09.01.2019	Sacubitril Valsartan Tablets, 49 mg /51 mg		49 mg/51 mg Tablet		12		Mean		53		69		77		84		88		Module 2	

		Batch No: DT1812065 Mfg Date: Dec-2018			(b)(4)				
		ENTRESTO (Sacubitril Valsartan) Film coated Tablets Lot No: FX000282 Exp Date: Jan-2021 Distributed By: Novartis pharmaceutical Corporation, East Hanover, NJ-07936	12	49 mg/51 mg Tablet					
	11.02.2019				10.9	8.4	9.2	8.9	
					59	78	90	94	
					(b)(4)				
					8.1	7.8	7.0	2.5	
Dissolution Conditions									
Apparatus:									
Speed of Rotation:									
Medium:									
Volume:									
Temperature:									
Firm's Proposed Specifications									
Dissolution Testing Site (Name, Address)					MSN Laboratories Private Limited – Formulations Division, Unit-II Survey Nos. 1277 & 1319 to 1324, Nandigama (Village) and (Mandal), Ranga Reddy District Pin Code-509228, Telangana, India				
Study Ref No.	Testing Date	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes)				Study Report Location
					10	15	20	30	45
					59	78	87	94	96
					(b)(4)				Module 2
DPR-18046-00	08.01.2019	Sacubitril Valsartan Tablets, 49 mg /51 mg Batch No: DT1812066 Mfg Date: Dec-2018	49 mg/51 mg Tablet	12	7.8	6.6	6.5	5.1	3.8

	11.02.2019	ENTRESTO (Sacubitril Valsartan) Film coated Tablets Lot No: FX000282 Exp Date: Jan-2021 Distributed By: Novartis pharmaceutical Corporation, East Hanover, NJ-07936	49 mg/51 mg Tablet	12	Mean	59	78	90	94	95
					Range	(b)(4)				
					%CV	8.1	7.8	7.0	3.9	2.5
Dissolution Conditions		Apparatus:								
		Speed of Rotation:								
		Medium:								
		Volume:		(b)(4)						
		Temperature:								
Firm's Proposed Specifications		(b)(4)								
Dissolution Testing Site (Name, Address)		MSN Laboratories Private Limited – Formulations Division, Unit-II Survey Nos. 1277 & 1319 to 1324, Nandigama (Village) and (Mandal), Ranga Reddy District Pin Code-509228, Telangana, India								
Study Ref No.	Testing Date	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)				Study Report Location
						10	15	20	30	45
					Mean	61	79	88	93	95
					Range	(b)(4)				
					%CV	20.0	13.6	10.5	7.5	5.4
					Mean	59	78	90	94	95
					Range	(b)(4)				
DPR-18046-00	09.01.2019	Sacubitril Valsartan Tablets, 49 mg /51 mg Batch No: DT1812067 Mfg Date: Dec-2018	49 mg/51 mg Tablet	12						Module 2
	11.02.2019	ENTRESTO (Sacubitril Valsartan) Film coated Tablets Lot No: FX000282	49 mg/51 mg Tablet	12						

		Exp Date: Jan-2021 Distributed By: Novartis pharmaceutical Corporation, East Hanover, NJ-07936			%CV	8.1	7.8	7.0	3.9	2.5
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VAL:

Dissolution Conditions		Apparatus:		(b)(4)							
		Speed of Rotation:									
		Medium:									
		Volume:									
		Temperature:									
Firm's Proposed Specifications				(b)(4)							
Dissolution Testing Site (Name, Address)				MSN Laboratories Private Limited – Formulations Division, Unit-II Survey Nos. 1277 & 1319 to 1324, Nandigama (Village) and (Mandal),Ranga Reddy District Pin Code-509228, Telangana, India							
Study Ref No.	Testing Date	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)				Study Report Location	
						10	15	20	30		45
						54	69	77	84		88
						(b)(4)					
DPR-18046-00	09.01.2019	Sacubitril Valsartan Tablets, 49 mg /51 mg Batch No: DT1812065 Mfg Date: Dec-2018	49 mg/51 mg Tablet	12	Mean	54	69	77	88	Module 2	
					Range	(b)(4)					
					%CV	10.2	8.0	9.0	8.6		6.1
	11.02.2019		49 mg/51 mg Tablet	12	Mean	60	80	92	96	97	

[Module 2](#)

		ENTRESTO (Sacubitril Valsartan) Film coated Tablets Lot No: FX000282 Exp Date: Jan-2021 Distributed By: Novartis pharmaceutical Corporation, East Hanover, NJ-07936			Range	(b)(4)						
Dissolution Conditions		Apparatus:	(b)(4)									
		Speed of Rotation:										
		Medium:										
		Volume:										
Firm's Proposed Specifications		Temperature:										
Dissolution Testing Site (Name, Address)		MSN Laboratories Private Limited – Formulations Division, Unit-II Survey Nos. 1277 & 1319 to 1324, Nandigama (Village) and (Mandal), Ranga Reddy District Pin Code-509228, Telangana, India										
Study Ref No.	Testing Date	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)			Study Report Location			
DPR-18046-00	08.01.2019	Sacubitril Valsartan Tablets, 49 mg /51 mg Batch No: DT1812066 Mfg Date: Dec-2018	49 mg/51 mg Tablet	12	Mean	10	15	20	30	45	95	
						59	78	87	93			
	11.02.2019					Range	(b)(4)					
							%CV	7.5	6.5	6.3	4.9	3.7
							Mean	60	80	92	96	97
					Range	(b)(4)						

[Module 2](#)

		Exp Date: Jan-2021 Distributed By: Novartis pharmaceutical Corporation, East Hanover, NJ-07936				%CV	8.0	7.6	6.7	3.7	2.3		
Dissolution Conditions			Apparatus:		(b)(4)								
			Speed of Rotation:										
			Medium:										
			Volume:										
			Temperature:										
Firm's Proposed Specifications			(b)(4)										
Dissolution Testing Site (Name, Address)			MSN Laboratories Private Limited – Formulations Division, Unit-II Survey Nos. 1277 & 1319 to 1324, Nandigama (Village) and (Mandal), Ranga Reddy District Pin Code-509228, Telangana, India										
Study Ref No.	Testing Date	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)					Study Report Location		
						10	15	20	30	45			
DPR-18046-00	09.01.2019	Sacubitril Valsartan Tablets, 49 mg /51 mg Batch No: DT1812067 Mfg Date: Dec-2018	49 mg/51 mg Tablet	12	Mean	61	79	88	93	95	Module 2		
					Range	(b)(4)							
					%CV	19.2	12.9	9.8	6.9	4.8			
	11.02.2019	ENTRESTO (Sacubitril Valsartan) Film coated Tablets Lot No: FX000282 Exp Date: Jan-2021 Distributed By: Novartis pharmaceutical Corporation, East Hanover, NJ-07936	49 mg/51 mg Tablet	12	Mean	60	80	92	96	97			
					Range	(b)(4)							
					%CV	8.0	7.6	6.7	3.7	2.3			

97 mg /103 mg:

SAC:

Dissolution Conditions		Apparatus:		(b)(4)									
		Speed of Rotation:											
		Medium:											
		Volume:											
		Temperature:											
Firm's Proposed Specifications													
Dissolution Testing Site (Name, Address)		MSN Laboratories Private Limited – Formulations Division, Unit-II Survey Nos. 1277 & 1319 to 1324, Nandigama (Village) and (Mandal), Ranga Reddy District Pin Code-509228, Telangana, India											
Study Ref No.	Testing Date	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)				Study Report Location			
						10	15	20	30		45		
DPR-18046-00	10.01.2019	Sacubitril Valsartan Tablets, 97 mg /103 mg Batch No: DT1812068 Mfg Date: Dec-2018	97 mg/103 mg Tablet	12	Mean	63	86	96	97	98	Module 2		
					Range	(b)(4)							
					%CV	14.2	10.0	7.5	4.5	3.4			
	Mean	50	70	85	94	97							
		Range	(b)(4)										
		%CV	8.1	7.9	8.3	5.2	2.3						
Dissolution Conditions		Apparatus:		(b)(4)									
		Speed of Rotation:											
		Medium:											
		Volume:											

Firm's Proposed Specifications		(b)(4)									
Dissolution Testing Site (Name, Address)		MSN Laboratories Private Limited – Formulations Division, Unit-II Survey Nos. 1277 & 1319 to 1324, Nandigama (Village) and (Mandal), Ranga Reddy District Pin Code-509228, Telangana, India									
Study Ref No.	Testing Date	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes)				Study Report Location		
					10	15	20	30		45	
DPR-18046-00	10.01.2019	Sacubitril Valsartan Tablets, 97 mg /103 mg Batch No: <u>DT1812069</u> Mfg Date: Dec-2018	97 mg/103 mg Tablet	12	Mean	63	88	99	102	102	
					Range	(b)(4)					
					%CV	8.2	5.9	2.1	1.4	1.1	
					Mean	50	70	85	94	97	
					Range	(b)(4)					
					%CV	8.1	7.9	8.3	5.2	2.3	
Dissolution Conditions		Apparatus: Speed of Rotation: Medium: Volume: Temperature: (b)(4)									
Firm's Proposed Specifications		(b)(4)									
Dissolution Testing Site (Name, Address)		MSN Laboratories Private Limited – Formulations Division, Unit-II Survey Nos. 1277 & 1319 to 1324, Nandigama (Village) and (Mandal), Ranga Reddy District Pin Code-509228, Telangana, India									
Study	Testing	Product ID \ Batch No.	Dosage	No. of	Collection Times (minutes)				Study		

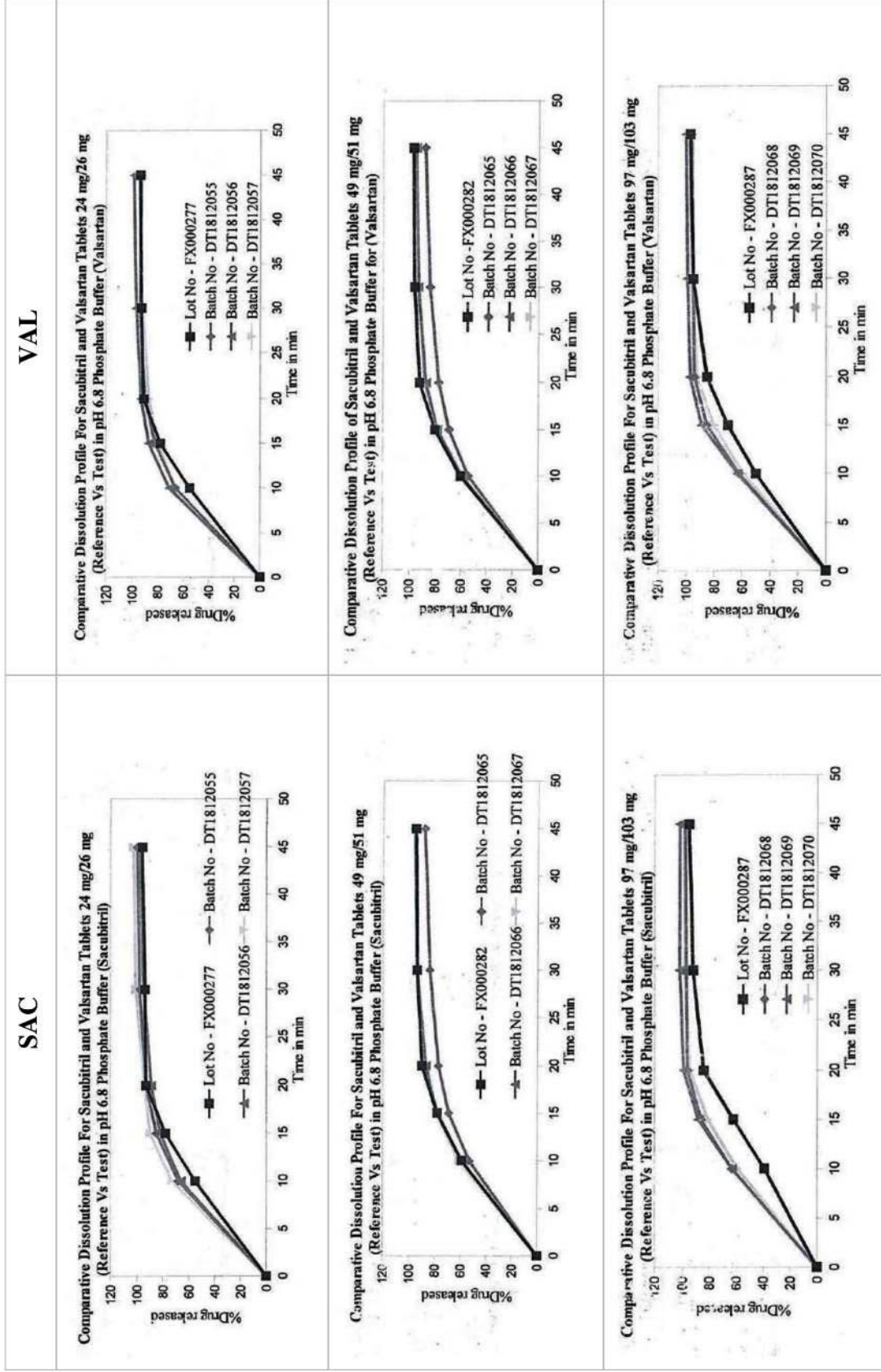
Ref No.	Date	(Test – Manufacture Date) (Reference – Expiration Date)	Strength & Form	Dosage Units		10	15	20	30	45	Report Location
DPR-18046-00	11.01.2019	Sacubitril Valsartan Tablets, 97 mg /103 mg Batch No: DT1812070 Mfg Date: Dec-2018	97 mg/103 mg Tablet	12	Mean	59	81	94	98	99	Module 2
					Range	(b)(4)					
					%CV	11.6	8.7	6.3	2.6	1.5	
	11.02.2019	ENTRESTO (Sacubitril Valsartan) Film coated Tablets Lot No: FX000287 Exp Date: Jan-2021 Distributed By: Novartis pharmaceutical Corporation, East Hanover, NJ-07936	97 mg/103 mg Tablet	12	Mean	50	70	85	94	97	
					Range	(b)(4)					
					%CV	8.1	7.9	8.3	5.2	2.3	

VAL:

Dissolution Conditions		Apparatus:		(b)(4)					Study Report Location
		Speed of Rotation:							
		Medium:							
		Volume:							
		Temperature:							
Firm's Proposed Specifications		MSN Laboratories Private Limited – Formulations Division, Unit-II Survey Nos. 1277 & 1319 to 1324, Nandigama (Village) and (Mandal),Ranga Reddy District Pin Code-509228, Telangana, India							
Dissolution Testing Site (Name, Address)									
Study Ref No.	Testing Date	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes)				Study Report Location
					10	15	20	30	

DPR-18046-00	10.01.2019	Sacubitril Valsartan Tablets, 97 mg /103 mg Batch No: <u>DT1812068</u> Mfg Date: Dec-2018	97 mg/103 mg Tablet	12	Mean	62	85	94	95	96	<u>Module 2</u>
					Range	(b)(4)					
					%CV	13.8	10.0	7.5	4.5	3.4	
					Mean	50	70	85	95	97	
					Range	(b)(4)					
	11.02.2019	ENTRESTO (Sacubitril Valsartan) Film coated Tablets Lot No: <u>FX000287</u> Exp Date: Jan-2021 Distributed By: Novartis pharmaceutical Corporation, East Hanover, NJ-07936	97 mg/103 mg Tablet	12	%CV	8.0	7.8	8.2	5.1	2.2	
Dissolution Conditions											
Apparatus:		(b)(4)									
Speed of Rotation:											
Medium:											
Volume:											
Temperature:											
Firm's Proposed Specifications											
Dissolution Testing Site (Name, Address)											
MSN Laboratories Private Limited – Formulations Division, Unit-II Survey Nos. 1277 & 1319 to 1324, Nandigama (Village) and (Mandal), Ranga Reddy District Pin Code-509228, Telangana, India											
Study Ref No.	Testing Date	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)					Study Report Location
						10	15	20	30	45	
DPR-18046-00	10.01.2019	Sacubitril Valsartan Tablets, 97 mg /103 mg Batch No: <u>DT1812069</u> Mfg Date: Dec-2018	97 mg/103 mg Tablet	12	Mean	63	86	97	99	100	<u>Module 2</u>
					Range	(b)(4)					
					%CV	8.2	5.9	2.1	1.2	1.0	

	11.02.2019	ENTRESTO (Sacubitril Valsartan) Film coated Tablets Lot No: FX000287 Exp Date: Jan-2021 Distributed By: Novartis pharmaceutical Corporation, East Hanover, NJ-07936	97 mg/103 mg Tablet	12	Mean	50	70	85	95	97		
					Range	(b)(4)						
					%CV	8.0	7.8	8.2	5.1	2.2		
Dissolution Conditions		Apparatus:										
		Speed of Rotation:										
		Medium:										
		Volume:		(b)(4)								
		Temperature:										
Firm's Proposed Specifications		(b)(4)										
Dissolution Testing Site (Name, Address)		MSN Laboratories Private Limited – Formulations Division, Unit-II Survey Nos. 1277 & 1319 to 1324, Nandigama (Village) and (Mandal), Ranga Reddy District Pin Code-509228, Telangana, India										
Study Ref No.	11.01.2019	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date) Sacubitril Valsartan Tablets, 97 mg /103 mg Batch No: DT1812070 Mfg Date: Dec-2018	Dosage Strength & Form 97 mg/103 mg Tablet	No. of Dosage Units 12		Collection Times (minutes)					Study Report Location	
						10	15	20	30	45		
						59	80	92	96	97		
						(b)(4)						
						Mean						
						Range						
DPR-18046-00	11.02.2019	ENTRESTO (Sacubitril Valsartan) Film coated Tablets Lot No: FX000287	97 mg/103 mg Tablet	12		11.4	8.7	6.3	2.6	1.5	Module 2	
						50	70	85	95	97		
						(b)(4)						
						Range						



4.3.3 F2 Metric

F2 metric calculated?	☐ Yes ☒ No
If no, reason why F2 not calculated	(b)(4)

*Note: mean Q value is (b)(4) for both analytes for the SAC/VAL 49 mg/51 mg strength exhibit batch # DT1812065 which is (b)(4) %.

Please comment on whether dissolution data are adequate to support requests submitted under 21 CFR 320.22(d)(2) or 320.24(b)(6).	Yes, under 320.22(d)(2)
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Overall Comments:

1. It is noted that the applicant submitted comparative dissolution testing on unexpired test and reference batches of the biostudy and biowaiver strengths using a dissolution test method (b)(4) that is not the same as the FDA-recommended method [USP Type I Basket, pH 6.8 Phosphate buffer (b)(4), 75 RPM, 900 mL volume, 37.0°C temperature]¹⁹.
2. The applicant's proposed dissolution method and specification are under separate assessment by the biopharmaceutics reviewer for quality control and stability purpose. Per GDRP, the biopharmaceutics quality review²⁰ is currently pending.
3. The test and reference products of all strengths are (b)(4) (for SAC/VAL 49 mg/51 mg strength exhibit batch # DT1812065, the mean Q value is (b)(4) for both analytes - which is (b)(4), and therefore, f2 calculation is not necessary for comparison purpose. The dissolution profiles of the bio-strength (i.e. SAC/VAL 97 mg/103 mg or 200 mg) vis-à-vis the lower (i.e. SAC/VAL 24 mg/26 mg or 50 mg, and SAC/VAL 49 mg/51 mg or 100 mg) strengths are comparable and thus adequate to support the biowaiver request under 21 CFR 320.22 (d)(2) for the lower biowaiver strengths of the test product. However, since the biopharmaceutics approval of the applicant's dissolution method and specification is currently pending, the decision to grant biowaiver from BE perspective also cannot be made at this time.

¹⁹ FDA Dissolution Database; search by "Sacubitril": https://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_SearchResults.cfm Date Updated 12/4/2019.
²⁰ GDRP; ANDA 213748; <https://panorama.fda.gov/task/view?ID=5d233ea50001478c6f043dc8962f52a2>; last accessed on 12/14/2019.

4.4 Attachments

4.4.1 Additional Studies (If applicable)

Are there any additional studies? (e.g. pilot, failed) If yes, please provide the location of report (complete/summary).	☒ Yes ☐ No 2 failed pilot studies: BA18647467- Pilot Fasting (\\cdsesub1\evsprod\anda213748\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\fast-pilot\ba18647467-study-report.pdf) BA18647468 - Pilot Fed (\\cdsesub1\evsprod\anda213748\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\fed-pilot\ba18647468-study-report.pdf)
Number of Subjects	BA18647467 (Fasting) and BA18647468 (Fed): 16 (dosed and completed)
Are the test formulations in the pilot/failed studies and pivotal studies similar?	☒ Yes, same formulation as the bio-batch ☐ No
What was the objective of pilot/failed study?	BA18647467: (1) To evaluate the oral bioavailability of Sacubitril and Valsartan Tablets 97 mg/103 mg with that of 'ENTRESTO™' (Sacubitril and Valsartan) Tablets 97 mg/103 mg in healthy, adult, human subjects under fasting conditions. (2) To monitor safety of the subjects. BA18647468: (1) To evaluate the oral bioavailability of Sacubitril and Valsartan Tablets 97 mg/103 mg with that of 'ENTRESTO™' (Sacubitril and Valsartan) Tablets 97 mg/103 mg in healthy, adult, human subjects under fed conditions.

	(2) To monitor safety of the subjects.
Please comment on reason(s) of failure.	The failure of the following studies is likely attributable to their small sample size (n = 16 completed for both pilot studies). • BA18647467: The 90% CI for SAC Cmax and 90% CI for VAL Cmax, AUCT, and AUCI exceeded the bounds of CI limits 0.8 to 1.25. • BA18647468: The 90% CI for SAC Cmax exceeded the bounds of the CI limits 0.8 to 1.25.

Table 2 (A) Summary of Bioavailability Studies (Sacubitril)-Fasting Study

Study Ref. No.	Study Objective	Study Design	Treatment (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (range))	(Mean Parameters $\pm$ SD) (% CV)						Study Report Location
					Cmax (μ g /mL)	Tmax (hr)	AUCt (μ g *hr/ mL)	AUCi (μ g *hr/ mL)	tHalf (hr)	Kel (1/hr)	
Study # BA18647 467	To evaluate the oral bioavailability of Sacubitril and Valsartan Tablets 97 mg/103 mg with that of 'ENTRESTO™' (Sacubitril and Valsartan) Tablets 97 mg/103 mg in healthy, adult, human subjects under fasting conditions. To monitor safety of the subjects.	An open label, randomized, two-period, two-treatment, two-sequence, crossover, balanced, single dose oral bioequivalence fasting, study design.	Test Product: Sacubitril and Valsartan Tablets 97 mg/103 mg, 1 $\times$ 97/103 mg, Oral, [Batch No.: FR&D/SAV/T181 1028]	16 dosed, 16 completed study (16 males) Age: 34 (25-44) years Healthy, adult, male subjects.	2.041 $\pm$ 0.833 (40.808)	0.500 (0.333-3.000)	2.453 $\pm$ 0.632 (25.783)	2.473 $\pm$ 0.634 (25.658)	0.747 $\pm$ 0.193 (25.895)	0.987 $\pm$ 0.247 (25.020)	Page no. 01 to 114 study report
			Reference Product: 'ENTRESTO™' (Sacubitril/Valsartan) Tablets 97 mg/103 mg, 1 $\times$ 97/103 mg, Oral, [Lot No.: FX000021]		2.022 $\pm$ 0.858 (42.458)	0.625 (0.333-4.000)	2.367 $\pm$ 0.554 (23.391)	2.396 $\pm$ 0.555 (23.169)	0.908 $\pm$ 0.429 (47.177)	0.865 $\pm$ 0.263 (30.347)	

Note: The mean age is calculated based on completed subjects. Tmax is presented as Median (Range).

Table 2 (B) Summary of Bioavailability Studies (Valsartan)-Fasting Study

Study Ref. No.	Study Objective	Study Design	Treatment (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (range))	(Mean Parameters $\pm$ SD) (%CV)						Study Report Location
					C _{max} (μ g /mL)	T _{max} (hr)	AUC _t (μ g *hr/ mL)	AUC _i (μ g *hr/ mL)	tHalf (hr)	K _{el} (1/hr)	
Study # BA18647 467	To evaluate the oral bioavailability of Sacubitril and Valsartan Tablets 97 mg/103 mg with that of 'ENTRESTO™' (Sacubitril and Valsartan) Tablets 97 mg/103 mg in healthy, adult, human subjects under fasting conditions. To monitor safety of the subjects.	An open label, randomized, two-period, two-treatment, two-sequence, crossover, balanced, single dose oral bioequivalence fasting, study design.	Test Product: Sacubitril and Valsartan Tablets 97 mg/103 mg, 1 $\times$ 97/103 mg, Oral, [Batch No.: FR&D/SAV/T181 1028]	16 dosed, 16 complete study (16 males) Age: 34 (25-44) years Healthy, adult, male subjects.	4.791 $\pm$ 2.059 (42.987)	1.500 (1.000-4.000)	29.919 $\pm$ 15.802 (52.815)	30.330 $\pm$ 15.914 (52.471)	6.768 $\pm$ 1.345 (19.872)	0.107 $\pm$ 0.023 (21.422)	Page no. 01 to 114 study report
			Reference Product: 'ENTRESTO™' (Sacubitril/Valsartan) Tablets 97 mg/103 mg, 1 $\times$ 97/103 mg, Oral, [Lot No.: FX000021]		4.526 $\pm$ 2.032 (44.884)	1.625 (1.250-4.000)	28.575 $\pm$ 15.144 (52.996)	28.937 $\pm$ 15.241 (52.669)	6.612 $\pm$ 1.193 (18.043)	0.109 $\pm$ 0.023 (21.123)	

Note: The mean age is calculated based on completed subjects. T_{max} is presented as Median (Range).

Table 2 (C) Summary of Bioavailability Studies (Sacubitril)-Fed Study

Study Ref. No.	Study Objective	Study Design	Treatment (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (range))	(Mean Parameters ± SD) (% CV)						Study Report Location
					Cmax (µg /mL)	Tmax (hr)	AUCt (µg *hr/ mL)	AUCi (µg *hr/ mL)	tHalf (hr)	Kel (1/hr)	
Study # BA1864 7468	To evaluate the oral bioavailability of Sacubitril and Valsartan Tablets 97 mg/103 mg with that of 'ENTRESTO™' (Sacubitril and Valsartan) Tablets 97 mg/103 mg in healthy, adult, human subjects under fed conditions. To monitor safety of the subjects.	An open label, randomized, two-period, two-treatment, two-sequence, crossover, balanced, single dose oral bioequivalence fed, study design.	Test Product: Sacubitril and Valsartan Tablets 97 mg/103 mg, 1× 97/103 mg, Oral, [Batch No.: FR&D/SAV/T181 1028]	16 dosed, 16 completed study (16 males) Age: 34 (22-42) years Healthy, adult, male subjects.	1.531 ± 0.601 (39.249)	2.000 (1.500-3.667)	2.664 ± 0.542 (20.350)	2.688 ± 0.541 (20.113)	0.703 ± 0.134 (19.038)	1.019 ± 0.185 (18.205)	Page no. 01 to 117 study report
			Reference Product: 'ENTRESTO™' (Sacubitril / Valsartan) Tablets 97 mg/103 mg, 1× 97/103 mg, Oral, [Lot No.: FX000021]		1.732 ± 0.49 (28.255)	1.750 (0.533-4.500)	2.742 ± 0.575 (20.979)	2.765 ± 0.580 (20.984)	0.799 ± 0.170 (21.229)	0.904 ± 0.185 (20.501)	

Note: The mean age is calculated based on completed subjects. Tmax is presented as Median (Range).

Table 2 (D) Summary of Bioavailability Studies (Valsartan)-Fed Study

Study Ref. No.	Study Objective	Study Design	Treatment (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age; mean (range))	(Mean Parameters ± SD) (%CV)						Study Report Location
					Cmax (µg/mL)	Tmax (hr)	AUCt (µg*hr/mL)	AUCi (µg*hr/mL)	tHalf (hr)	Kel (1/hr)	
Study # BA18647 468	To evaluate the oral bioavailability of Sacubitril and Valsartan Tablets 97 mg/103 mg with that of 'ENTRESTO™' (Sacubitril and Valsartan) Tablets 97 mg/103 mg in healthy, adult, human subjects under fed conditions. To monitor safety of the subjects.	An open label, randomized, two-period, two-treatment, two-sequence, crossover, balanced, single dose oral bioequivalence fed, study design.	Test Product: Sacubitril and Valsartan Tablets 97 mg/103 mg, 1× 97/103 mg, Oral, [Batch No.: FR&D/SAV/T181 1028]	16 dosed, 16 complete study (16 males) Age: 34 (22-42) years Healthy, adult, male subjects.	3.635 ± 0.766 (21.068)	3.167 (2.333-5.000)	23.633 ± 6.644 (28.115)	24.038 ± 6.673 (27.760)	6.677 ± 0.985 (14.748)	0.106 ± 0.018 (17.251)	Page no. 01 to 117 study report
			Reference Product: 'ENTRESTO™' (Sacubitril / Valsartan) Tablets 97 mg/103 mg, 1× 97/103 mg, Oral, [Lot No.: FX000021]		3.741 ± 0.871 (23.290)	3.000 (2.000-5.000)	24.555 ± 5.327 (21.694)	24.917 ± 5.331 (21.396)	6.340 ± 1.219 (19.233)	0.114 ± 0.025 (21.667)	

Note: The mean age is calculated based on completed subjects. Tmax is presented as Median (Range).

Table 3 (A1) Statistical Summary of the Comparative Bioavailability Data for Unscaled Average BE studies (Sacubitril)

Reference Scaled Average Bioequivalence Approach Used ☐ Yes ☒ No						
If No, then complete Table 3A1 only						
If Yes, then complete Tables 3A1 and 3B						
Sacubitril and Valsartan Tablets (No of subjects completed= 16) 1x 97/103 mg Least Square Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fasting Bioequivalence Study (BA18647467)						
Parameter	Test	N	RLD	N	Ratio	90% CI
AUCt	2.383	16	2.315	16	102.94%	(97.38%;108.81%)
AUCi	2.403	16	2.344	16	102.52%	(97.01%;108.34%)
Cmax	1.910	16	1.869	16	102.23%	(80.79%;129.35%)
Sacubitril and Valsartan Tablets (No of subjects completed= 16) 1x 97/103 mg Least Square Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fed Bioequivalence Study (BA18647468)						
Parameter	Test	N	RLD	N	Ratio	90% CI
AUCt	2.606	16	2.675	16	97.44%	(93.02%;102.06%)
AUCi	2.632	16	2.697	16	97.58%	(93.12%;102.25%)
Cmax	1.417	16	1.642	16	86.29%	(73.17%;101.77%)

Table 3 (A2) Statistical Summary of the Comparative Bioavailability Data for Unscaled Average BE studies (Valsartan)

Reference Scaled Average Bioequivalence Approach Used ☐ Yes ☒ No						
If No, then complete Table 3A2 only						
If Yes, then complete Tables 3A2 and 3B						
Sacubitril and Valsartan Tablets (No of subjects completed= 16) 1x 97/103 mg Least Square Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fasting Bioequivalence Study (BA18647467)						
Parameter	Test	N	RLD	N	Ratio	90% CI
AUCt	25.923	16	23.954	16	108.22%	(78.61%;148.98%)
AUCi	26.370	16	24.437	16	107.91%	(79.34%;146.76%)
Cmax	4.370	16	3.906	16	111.88%	(80.57%;155.37%)

Sacubitril and Valsartan Tablets (No of subjects completed= 16) 1x 97/103 mg Least Square Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fed Bioequivalence Study (BA18647468)						
Parameter	Test	N	RLD	N	Ratio	90% CI
AUC_t	22.866	16	24.055	16	95.06%	(88.21%;102.43%)
AUC_i	23.276	16	24.421	16	95.31%	(88.68%;102.44%)
C_{max}	3.563	16	3.646	16	97.72%	(90.11%;105.97%)

Table 4 (A) Bioanalytical Method Validation: Sacubitril-Fasting Study- BA18647467

Information Requested	Data
Bioanalytical method validation report location	Module 5/ 5.3.1.4/ Method validation report of Sacubitril and Valsartan/ Page 01 to 119
Analyte	Sacubitril
Internal standard (IS)	Sacubitril D4
Method description	(b)(4)
Limit of quantitation	0.01000 µg/mL
Average recovery of drug (%)	88.2%
Average recovery of IS (%)	90.6%
Standard curve concentrations (µg/mL)	0.01000, 0.02000, 0.04000, 0.1000, 0.3000, 0.6000, 1.200, 2.400, 4.800 and 6.000
QC concentrations (µg/mL)	0.03000, 0.3600, 2.100 and 4.500
QC Intraday precision range (%)	0.5% to 1.7% (Intra run)
QC Intraday accuracy range (%)	89.8% to 96.4% (Intra run)
QC Interday precision range (%)	1.7% to 2.5% (Inter run)
QC Interday accuracy range (%)	92.5% to 94.7% (Inter run)
Bench-top stability (hrs)	27 hours at room temperature (15°C to 30°C) (For Sacubitril) 27 hours at room temperature (15°C to 30°C) [For Sacubitril fortified with Sacubitril (LBQ657) and 4-Hydroxy Valsartan (6.000/12.00 µg/mL)]
Stock stability (days)	34 days for analyte and internal standard at refrigerator temperature (2°C to 10°C)
Processed stability (hrs)	119 hours at room temperature (15°C to 30°C) and at refrigerator temperature (2°C to 10°C)

Freeze-thaw stability (cycles)	6 freeze thaw cycles (For Sacubitril) 6 freeze thaw cycles [For Sacubitril fortified with Sacubitril (LBQ657) and 4-Hydroxy Valsartan (6.000/12.00 µg/mL)]
Long-term storage stability (days)	97 days at -20°C±10°C Temperature (For Sacubitril) 98 days at -20°C±10°C Temperature [For Sacubitril fortified with Sacubitril (LBQ657) and 4-Hydroxy Valsartan (6.000/12.00 µg/mL)]
Dilution integrity	48.00 µg/mL, diluted 10 times 9.000 µg/mL, diluted 02 times
Selectivity	No significant interfering peak noted in blank plasma samples

Table 4 (B) Bioanalytical Method Validation: Valsartan- Fasting Study-BA18647467

Information Requested	Data
Bioanalytical method validation report location	Module 5/ 5.3.1.4/ Method validation report of Sacubitril and Valsartan/ Page 01 to 119
Analyte	Valsartan
Internal standard (IS)	Valsartan D9
Method description	(b)(4)
Limit of quantitation	0.02000 µg/mL
Average recovery of drug (%)	92.1%
Average recovery of IS (%)	93.1%
Standard curve concentrations (µg/mL)	0.02000, 0.04000, 0.08000, 0.2000, 0.6000, 1.200, 2.400, 4.800, 9.600 and 12.00
QC concentrations (µg/mL)	0.06000, 0.7200, 4.200 and 9.000
QC Intraday precision range (%)	0.3% to 1.9% (Intra run)
QC Intraday accuracy range (%)	96.8% to 105% (Intra run)
QC Interday precision range (%)	1.3% to 2.8% (Inter run)
QC Interday accuracy range (%)	99.5% to 102% (Inter run)
Bench-top stability (hrs)	27 hours at room temperature (15°C to 30°C) (For Valsartan) 27 hours at room temperature (15°C to 30°C) [For Valsartan fortified with Sacubitril (LBQ657) and 4-Hydroxy Valsartan (6.000/12.00 µg/mL)]
Stock stability (days)	34 days for analyte and 23 days for internal standard at refrigerator temperature (2°C to 10°C)

Processed stability (hrs)	119 hours at room temperature (15°C to 30°C) and at refrigerator temperature (2°C to 10°C)
Freeze-thaw stability (cycles)	6 freeze thaw cycles (For Valsartan) 6 freeze thaw cycles [For Valsartan fortified with Sacubitril (LBQ657) and 4-Hydroxy Valsartan (6.000/12.00 µg/mL)]
Long-term storage stability (days)	97 days at -20°C±10°C Temperature (For Valsartan) 98 days at -20°C±10°C Temperature [For Valsartan fortified with Sacubitril (LBQ657) and 4-Hydroxy Valsartan (6.000/12.00 µg/mL)]
Dilution integrity	96.00 µg/mL, diluted 10 times 18.00 µg/mL, diluted 02 times
Selectivity	No significant interfering peak noted in blank plasma samples

Table 4 (C) Bioanalytical Method Validation: Sacubitril-Fed Study-BA18647468

Information Requested	Data
Bioanalytical method validation report location	Module 5/ 5.3.1.4/ Method validation report of Sacubitril and Valsartan/ Page 01 to 119
Analyte	Sacubitril
Internal standard (IS)	Sacubitril D4
Method description	(b)(4)
Limit of quantitation	0.01000 µg/mL
Average recovery of drug (%)	88.2%
Average recovery of IS (%)	90.6%
Standard curve concentrations (µg/mL)	0.01000, 0.02000, 0.04000, 0.1000, 0.3000, 0.6000, 1.200, 2.400, 4.800 and 6.000
QC concentrations (µg/mL)	0.03000, 0.3600, 2.100 and 4.500
QC Intraday precision range (%)	0.5% to 1.7% (Intra run)
QC Intraday accuracy range (%)	89.8% to 96.4% (Intra run)
QC Interday precision range (%)	1.7% to 2.5% (Inter run)
QC Interday accuracy range (%)	92.5% to 94.7% (Inter run)
Bench-top stability (hrs)	27 hours at room temperature (15°C to 30°C) (For Sacubitril) 27 hours at room temperature (15°C to 30°C) [For Sacubitril fortified with Sacubitril (LBQ657) and 4-Hydroxy Valsartan (6.000/12.00 µg/mL)]

Stock stability (days)	34 days for analyte and internal standard at refrigerator temperature (2°C to 10°C)
Processed stability (hrs)	119 hours at room temperature (15°C to 30°C) and at refrigerator temperature (2°C to 10°C)
Freeze-thaw stability (cycles)	6 freeze thaw cycles (For Sacubitril) 6 freeze thaw cycles [For Sacubitril fortified with Sacubitril (LBQ657) and 4-Hydroxy Valsartan (6.000/12.00 µg/mL)]
Long-term storage stability (days)	97 days at -20°C±10°C Temperature (For Sacubitril) 98 days at -20°C±10°C Temperature [For Sacubitril fortified with Sacubitril (LBQ657) and 4-Hydroxy Valsartan (6.000/12.00 µg/mL)]
Dilution integrity	48.00 µg/mL, diluted 10 times 9.000 µg/mL, diluted 02 times
Selectivity	No significant interfering peak noted in blank plasma samples

Table 4 (D) Bioanalytical Method Validation: Valsartan-Fed Study-BA18647468

Information Requested	Data
Bioanalytical method validation report location	Module 5/ 5.3.1.4/ Method validation report of Sacubitril and Valsartan/ Page 01 to 119
Analyte	Valsartan
Internal standard (IS)	Valsartan D9
Method description	(b)(4)
Limit of quantitation	0.02000 µg/mL
Average recovery of drug (%)	92.1%
Average recovery of IS (%)	93.1%
Standard curve concentrations (µg/mL)	0.02000, 0.04000, 0.08000, 0.2000, 0.6000, 1.200, 2.400, 4.800, 9.600 and 12.00
QC concentrations (µg/mL)	0.06000, 0.7200, 4.200 and 9.000
QC Intraday precision range (%)	0.3% to 1.9% (Intra run)
QC Intraday accuracy range (%)	96.8% to 105% (Intra run)
QC Interday precision range (%)	1.3% to 2.8% (Inter run)
QC Interday accuracy range (%)	99.5% to 102% (Inter run)
Bench-top stability (hrs)	27 hours at room temperature (15°C to 30°C) (For Valsartan) 27 hours at room temperature (15°C to 30°C) [For Valsartan fortified with Sacubitril (LBQ657) and 4-Hydroxy Valsartan (6.000/12.00 µg/mL)]

Stock stability (days)	34 days for analyte and 23 days for internal standard at refrigerator temperature (2°C to 10°C)
Processed stability (hrs)	119 hours at room temperature (15°C to 30°C) and at refrigerator temperature (2°C to 10°C)
Freeze-thaw stability (cycles)	6 freeze thaw cycles (For Valsartan) 6 freeze thaw cycles [For Valsartan fortified with Sacubitril (LBQ657) and 4-Hydroxy Valsartan (6.000/12.00 µg/mL)]
Long-term storage stability (days)	97 days at -20°C±10°C Temperature (For Valsartan) 98 days at -20°C±10°C Temperature [For Valsartan fortified with Sacubitril (LBQ657) and 4-Hydroxy Valsartan (6.000/12.00 µg/mL)]
Dilution integrity	96.00 µg/mL, diluted 10 times 18.00 µg/mL, diluted 02 times
Selectivity	No significant interfering peak noted in blank plasma samples

Table 5 Summary of In Vitro Dissolution Studies

Table 5.1: Sacubitril and Valsartan Tablets, 97 mg/ 103 mg, Batch No: FR&D/SAV/TI811028- For Sacubitril

Dissolution Conditions			Apparatus:											
			Speed of Rotation:											
			Medium:		(b)(4)									
			Volume:											
			Temperature:											
Firm's Proposed Specifications					(b)(4)									
Dissolution Testing Site (Name, Address)			MSN Laboratories Private limited, R & D Centre, Plot NO.12, Phase-IV, Sy. No. 119 to 140, 258,,275 to 280, IDA, Pashamylaram(Village), Patancheru(Mandal), Sangareddy Dist-502307, Telangana, India											
Study Ref No.	Testing Date	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)				Study Report Location				
						10	15	20	30		45			
CDR/S AV-T- 004-00	20/11/2018	Sacubitril and Valsartan Tablets, 97 mg/ 103 mg Batch No: FR&D/SAV/TI811028 Mfg Date: Nov-2018	97 mg/103 mg Tablet	06		Mean	53	73	83	90	94	Module 2		
						Range								
						%CV	12.8	14.0	11.4	8.3	3.8			
	01/09/2018	ENTRESTO® (Sacubitril and Valsartan) Tablets Lot No: FX000021 Exp Date: April-2020	97 mg/ 103 mg Tablet	06		Mean	56	76	91	99	101			
						Range								
						%CV	7.1	7.4	6.2	5.2	3.3			

Table 5.2: Sacubitril and Valsartan Tablets, 97 mg/ 103 mg, Batch No: FR&D/SAV/TI811028- For Valsartan

Dissolution Conditions		Apparatus:		(b)(4)							
		Speed of Rotation:									
		Medium:									
		Volume:									
		Temperature:									
Firm's Proposed Specifications											
Dissolution Testing Site (Name, Address)		MSN Laboratories Private limited, R & D Centre, Plot NO.12, Phase-IV, Sy. No. 119 to 140, 258,,275 to 280, IDA, Pashamylaram(Village), Patancheru(Mandal), Sangareddy Dist-502307, Telangana, India									
Study	Testing	Product ID \ Batch No.	Dosage	No. of	Collection Times (minutes)			Study			

Ref No.	Date	(Test – Manufacture Date) (Reference – Expiration Date)	Strength & Form	Dosage Units		10	15	20	30	45	Report Location
CDR/S AV-T- 004-00	20/11/2018	Sacubitril and Valsartan Tablets, 97 mg/ 103 mg Batch No: FR&D/SAV/T1811028 Mfg Date: Nov-2018	97 mg/103 mg Tablet	06	Mean	53	73	82	89	93	Module 2
					Range						
					%CV	12.0	13.4	10.7	7.5	3.1	
	01/09/2018	ENTRESTO® (Sacubitril and Valsartan) Tablets Lot No: FX000021 Exp Date: April-2020	97 mg/ 103 mg Tablet	06	Mean	55	75	90	98	100	
					Range						
					%CV	7.3	7.0	6.2	5.0	2.9	

Table 6 Formulation Data

Ingredient	Amount (mg) / Tablet	Amount (%) / Tablet
	Sacubitril and Valsartan Tablets, 97 mg/ 103 mg	Sacubitril and Valsartan Tablets, 97 mg/ 103 mg
(b)(4)		
Sacubitril and Valsartan	(b)(4)	(b)(4)
Microcrystalline Cellulose (b)(4) USP-NF		
Crospovidone (b)(4) USP-NF		
Croscarmellose Sodium (b)(4) USP-NF		
Colloidal Silicon Dioxide (b)(4) USP-NF		
Talc (b)(4) USP		
Magnesium Stearate (b)(4) USP-NF		
(b)(4)	(b)(4)	(b)(4)
(b)(4)		
Total	412.000	100.00
(b)(4)		

Table 7 Demographic Profile of Subjects Completing the Bioequivalence Study**Table 7 (a) Fasting Study-BA18647467**

Study No. BA18647467			
		Treatment Groups	
		Test Product (T) N = 16	Reference Product (R) N = 16
Age (years)	Mean ± SD	34 (± 7)	34 (± 7)
	Range	25 - 44	25 - 44
Age Groups	< 18	00 (0%)	00 (0%)
	18 – 40	13 (81.25%)	13 (81.25%)
	41 – 64	03 (18.75%)	03 (18.75%)
	65 – 75	00 (0%)	00 (0%)
	> 75	00 (0%)	00 (0%)
Sex	Male	16 (100%)	16 (100%)

	Female	00 (0%)	00 (0%)
Race	Asian	16 (100%)	16 (100%)
	Black	00 (0%)	00 (0%)
	Caucasian	00 (0%)	00 (0%)
	Hispanic	00 (0%)	00 (0%)
	Other	00 (0%)	00 (0%)
BMI (Kg/m ²)	Mean $\pm$ SD	23.4 ($\pm$ 3.6)	23.4 ($\pm$ 3.6)
	Range	18.6 – 29.4	18.6 – 29.4

Table 7 (b) Fed Study-BA18647468

Study No. BA18647468			
		Treatment Groups	
		Test Product (T) N = 16	Reference Product (R) N = 16
Age (years)	Mean $\pm$ SD	34 ($\pm$ 6)	34 ($\pm$ 6)
	Range	22 - 42	22 - 42
Age Groups	< 18	00 (0%)	00 (0%)
	18 – 40	15 (93.75%)	15 (93.75%)
	41 – 64	01 (6.25%)	01 (6.25%)
	65 – 75	00 (0%)	00 (0%)
	> 75	00 (0%)	00 (0%)
Sex	Male	16 (100%)	16 (100%)
	Female	00 (0%)	00 (0%)
Race	Asian	16 (100%)	16 (100%)
	Black	00 (0%)	00 (0%)
	Caucasian	00 (0%)	00 (0%)
	Hispanic	00 (0%)	00 (0%)
	Other	00 (0%)	00 (0%)
BMI (Kg/m ²)	Mean $\pm$ SD	23.2 ($\pm$ 2.9)	23.2 ($\pm$ 2.9)
	Range	19.8 - 27.9	19.8 - 27.9

Table 8 Incidence of Adverse Events in Individual Studies

Table 8 (a) Fasting Study-BA18647467

There were no adverse events reported during conduct of the study.

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Fasted Bioequivalence Study Study No. BA18647467	
	Test (T)	Reference (R)
NONE		

Table 8 (b) Fed study-BA18647468

(1) Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Fed Bioequivalence Study Study No. BA18647468	
	Test (T) (2) N=16 (3) n (%)	Reference (R) (2) N=16 (3) n (%)
Investigations	-	-
Alanine amino transferase increased	-	01 (6.25%)
Aspartate amino transferase increased	-	01(6.25%)
Total	-	01 (6.25%)

(1) MedDRA Version 21.1

(2) N=Number of subjects dosed for each treatment

(3) n= Number of subjects reporting at least one incidence of respective adverse event; (%)=percentage of subjects reporting at least one incidence of respective adverse event.

Table 9 Reanalysis of Study Samples:**Table 9a Sacubitril (Fasting Study-BA18647467)**

Study No. BA18647467 Additional information in Module 5/Section 5.3.1.4/ Final Summary Report/ Page 18 of 90								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0.00	0.00	0	0	0.00	0.00
Low internal standard	0	1	0.00	0.26	0	1	0.00	0.26
Total	0	1	0.00	0.26	0	1	0.00	0.26

Note: Total number of samples assayed = 768

Total number of samples assayed for Test Product (T) = 384

Total number of samples assayed for Reference Product (R) = 384

Table 9b Valsartan (Fasting Study-BA18647467)

Study No. BA18647467 Additional information in Module 5/Section 5.3.1.4/ Final Summary Report/ Page 18 of 90								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0.00	0.00	0	0	0.00	0.00

Low internal standard	0	1	0.00	0.26	0	1	0.00	0.26
Total	0	1	0.00	0.26	0	1	0.00	0.26

Note: Total number of samples assayed = 768
Total number of samples assayed for Test Product (T) = 384
Total number of samples assayed for Reference Product (R) = 384

Table 9c Sacubitril (Fed Study-BA18647468)

Study No. BA18647468 Additional information in Module 5/Section 5.3.1.4/ Final Summary Report/ Page 18 of 92								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0.00	0.00	0	0	0.00	0.00
Internal standard added inadvertently	0	1	0.00	0.25	0	0	0.00	0.00
Total	0	1	0.00	0.25	0	0	0.00	0.00

Note: Total number of samples assayed = 800
Total number of samples assayed for Test Product (T) = 400
Total number of samples assayed for Reference Product (R) = 400

Table 9d Valsartan (Fed Study-BA18647468)

Study No. BA18647468 Additional information in Module 5/Section 5.3.1.4/ Final Summary Report/ Page 18 of 92								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0.00	0.00	0	0	0.00	0.00
Internal standard added inadvertently	0	1	0.00	0.25	0	0	0.00	0.00
Total	0	1	0.00	0.25	0	0	0.00	0.00

Note: Total number of samples assayed = 800
Total number of samples assayed for Test Product (T) = 400
Total number of samples assayed for Reference Product (R) = 400

Table 10 Study Information

Table 10a Fasting Study-BA18647467

Study Number	BA18647467
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Study Title	Single dose oral bioequivalence pilot study of Sacubitril and Valsartan Tablets 97 mg/103 mg and 'ENTRESTO™' (Sacubitril and Valsartan) Tablets 97 mg/103 mg in healthy adult human subjects under fasting conditions.
Study Type	☒ In Vivo ☐ BE In Vitro ☐ BE Permeability ☐ Other
Submission Location: o Study Report o Validation Report o Bioanalytical Report	location, 5.3.1.2 location, 5.3.1.4 location, 5.3.1.4
Clinical Site (Name, Address, Phone #, Fax #)	Cliantha Research Limited Sigma-1 Corporate, B/H Rajpath Club, Opposite Mann Party Plot Off. S.G. Highway, Bodakdev, Ahmedabad-380 054, Gujarat, India Tel# +91 - 79 - 66135601 Fax# +91 - 79 - 66135602 FEI: 3009853705 DUNS: 860037958
Principal Clinical Investigator (Name, Email)	Dr. Mayur Soni, MBBS msoni@cliantha.in & pi@cliantha.in
Dosing Dates:	Period I: 15 Nov 18 Period II: 24 Nov 18
Analytical Site (Name, Address, Phone #, Fax #)	(b)(4)
Principal Analytical Investigator (Name, Email)	
Analytical dates	For Sacubitril: 28 Nov 18 to 06 Dec 18 For Valsartan: 28 Nov 18 to 06 Dec 18
Sample Storage : (a) Duration (no. of days from the first day of sample collection to the last day of sample analysis) (b) Temperature Range (e.g., -20° C to -80° C)	(a) 21 days from 15 Nov 18 to 06 Dec 18 (Sacubitril and Valsartan) (b) -20°C±10°C temperature (Sacubitril and Valsartan)
Long-Term Storage Stability Coverage (no. days @ temp °C)	97 days at -20°C±10°C Temperature (For Sacubitril and Valsartan) 98 days at -20°C±10°C Temperature [For Sacubitril and Valsartan fortified with Sacubitril (LBQ657) and 4-Hydroxy Valsartan (6.000/ 12.00 µg/mL)]
LTSS Data Location	Module 5/Section 5.3.1.4/ Method Validation Report of Sacubitril and Valsartan/ Addendum-II to the Method Validation Report of Sacubitril and Valsartan/ Section 4.1 and Section 4.2/ Page 409 of 482 (For Sacubitril and Valsartan)

	Module 5/Section 5.3.1.4/ Method Validation Report of Sacubitril and Valsartan/ Addendum-II to the Method Validation Report of Sacubitril and Valsartan / Section 4.1 and Section 4.2/ Page 409 and 410 of 482 [For Sacubitril and Valsartan fortified with Metabolite Sacubitrilat (LBQ657) and 4-Hydroxy Valsartan (6.000/12.00 µg/mL)]
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Table 10b Fed Study-BA18647468

Study Number	BA18647468	
Study Title	Single dose oral bioequivalence pilot study of Sacubitril and Valsartan Tablets 97 mg/103 mg and 'ENTRESTO™' (Sacubitril and Valsartan) Tablets 97 mg/103 mg in healthy adult human subjects under fed conditions.	
Study Type	☒ In Vivo ☐ BE In Vitro ☐ BE Permeability ☐ Other	
Submission Location: o Study Report o Validation Report o Bioanalytical Report	location, 5.3.1.2 location, 5.3.1.4 location, 5.3.1.4	
Clinical Site (Name, Address, Phone #, Fax #)	Cliantha Research Limited Sigma-1 Corporate, B/H Rajpath Club, Opposite Mann Party Plot Off. S.G. Highway, Bodakdev, Ahmedabad-380 054, Gujarat, India Tel# +91 - 79 – 66135601 Fax# +91 - 79 – 66135602 FEI: 3009853705 DUNS: 860037958	
Principal Clinical Investigator (Name, Email)	Dr. Mayur Soni, MBBS msoni@cliantha.in & pi@cliantha.in	
Dosing Dates:	Period I: 20 Nov 18 Period II: 27 Nov 18	
Analytical Site (Name, Address, Phone #, Fax #)	(b)(4)	
Principal Analytical Investigator (Name, Email)		
Analytical dates	For Sacubitril: 01 Dec 18 to 12 Dec 18 For Valsartan: 01 Dec 18 to 12 Dec 18	
Sample Storage : (a) Duration (no. of days from the first day of sample collection to the last day of sample analysis) (b) Temperature Range (e.g.,	(a) 22 days from 20 Nov 18 to 12 Dec 18 (For Sacubitril and Valsartan) (b) -20°C±10°C temperature (For Sacubitril and Valsartan)	

-20° C to -80° C)	
Long-Term Storage Stability Coverage (no. days @ temp °C)	97 days at -20°C±10°C Temperature (For Sacubitril and Valsartan) 98 days at -20°C±10°C Temperature [For Sacubitril and Valsartan each fortified with Sacubitril (LBQ657) and 4-Hydroxy Valsartan (6.000/ 12.00 µg/mL)]

Table 11 Product Information

Product	Test	Reference
Treatment ID	T	R
Product Name	Sacubitril and Valsartan Tablets 97 mg/103 mg	'ENTRESTO™' (Sacubitril/ Valsartan) Tablets 97 mg/103 mg
Manufacturer	MSN Laboratories Private Ltd., India	Manufactured By : (b)(4) Distributed By: Novartis Pharmaceuticals Corporation, East Hanover, New Jersey 07936
Batch/Lot No.	Batch No. FR&D/SAV/T1811028	Lot No. FX000021
Manufacture Date	Nov 2018	Not Applicable
Expiration Date	Not Applicable	Apr 2020
Strength	97 mg/103 mg	97 mg/103 mg
Dosage Form	Tablets	Tablets
Bio-batch Size	(b)(4)	Not Applicable
Production Batch Size		Not Applicable
Potency	Sacubitril: 98.5 % Valsartan: 96.8 %	Sacubitril: 98.0 % Valsartan: 100.2 %
Content Uniformity (mean, % CV)	Sacubitril: Mean: 101.9 %CV: 2.96	Not Applicable
	Valsartan: Mean: 97.6 %CV: 3.06	Not Applicable
Dose Administered	1 x 97 mg/103 mg	1 x 97 mg/103 mg
Route of Administration	Oral	Oral

Table 12 Dropout Information

Table 12a Fasting Study BA18647467

There were no discontinued subjects during the entire study.

Study No. BA18647467				
Subject No	Reason for dropout/replacement	Period	Replaced?	Replaced with
NONE				

Table 12b Fed Study-BA18647468

Study No. BA18647468				
Subject No	Reason for dropout/replacement	Period	Replaced?	Replaced with
(b)(6)	Reason: Withdrawal by subject. Date: Time: 1414 hours	NA	Yes	(b)(6)

Table 13 Protocol Deviations**Table 13a Fasting Study-BA18647467**

Study No. BA18647467		
Type	Subject #s (Test) (T)	Subject #s (Reference) (R)
Blood draw time point deviations, Period I	NA	(b)(6)

Table 13b Fed Study-BA18647468

Study No. BA18647468		
Type	Subject #s (Test) (T)	Subject #s (Reference) (R)
Blood draw time point deviations, Period I		NA

Table 14 Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses**Table 14a Sacubitril (Fasting Study-BA18647467)**

Bioequivalence Study No. BA18647467 Sacubitril										
Parameter	Standard Curve Samples									
Concentration (µg/mL)	0.01000	0.02000	0.04000	0.1000	0.3000	0.6000	1.200	2.400	4.800	6.000
*Inter day Precision (%CV)	2.6	5.2	4.5	2.6	3.9	3.2	1.6	2.4	3.7	2.9
*Inter day Accuracy (%Actual	98.1	101	103	103	103	102	99.9	99.0	95.9	94.4
Linearity (r ² value)	0.9945492 – 0.9989797									
Linearity Range (µg/mL)	0.01000 – 6.000									
Sensitivity/LOQ (µg/mL)	0.01000									
Bioequivalence Study No. BA18647467 Sacubitril										

Parameter	Quality Control Samples			
Concentration (µg/mL)	LQC 0.03000	MQC-2 0.3600	MQC-1 2.100	HQC 4.500
*Inter day Precision (%CV)	3.4	3.1	3.9	4.3
*Inter day Accuracy (%Actual)	99.2	103	100	98.7

Note: * = Results are reported as inter run.

Table 14b Valsartan (Fasting Study-BA18647467)

Bioequivalence Study No. BA18647467 Valsartan										
Parameter	Standard Curve Samples									
Concentration (µg/mL)	0.02000	0.04000	0.08000	0.2000	0.6000	1.200	2.400	4.800	9.600	12.00
*Inter day Precision (%CV)	1.0	1.8	3.9	5.0	3.0	2.9	3.5	2.2	3.4	3.9
*Inter day Accuracy (%Actual)	98.4	102	99.9	104	103	102	102	97.6	96.6	94.2
Linearity (r ² value)	0.9946965 – 0.9987314									
Linearity Range (µg/mL)	0.02000 – 12.00									
Sensitivity/LOQ (µg/mL)	0.02000									
Bioequivalence Study No. BA18647467 Valsartan										
Parameter	Quality Control Samples									
Concentration (µg/mL)	LQC 0.06000		MQC-2 0.7200		MQC-1 4.200			HQC 9.000		
*Inter day Precision (%CV)	4.4		4.5		3.9			3.6		
*Inter day Accuracy (%Actual)	99.6		103		99.1			98.2		

Note: * = Results are reported as inter run.

Table 14c Sacubitril (Fed Study-BA18647468)

Bioequivalence Study No. BA18647468 Sacubitril										
Parameter	Standard Curve Samples									
Concentration (µg/mL)	0.01000	0.02000	0.04000	0.1000	0.3000	0.6000	1.200	2.400	4.800	6.000
*Inter day Precision (%CV)	1.6	1.7	3.0	2.8	2.6	2.7	1.3	2.4	3.8	3.5

*Inter day Accuracy (%Actual)	96.7	103	105	103	105	104	99.8	96.8	94.9	92.0
Linearity (r ² value)	0.9937432 – 0.9995399									
Linearity Range (µg/mL)	0.01000 – 6.000									
Sensitivity/LOQ (µg/mL)	0.01000									
Bioequivalence Study No. BA18647468										
Sacubitril										
Parameter	Quality Control Samples									
Concentration (µg/mL)	LQC 0.03000		MQC-2 0.3600		MQC-1 2.100			HQC 4.500		
*Inter day Precision (%CV)	3.9		2.8		2.9			3.3		
*Inter day Accuracy (%Actual)	100		105		98.3			95.4		

Note: * = Results are reported as inter run.

Table 14d Valsartan (Fed Study-BA18647468)

Bioequivalence Study No. BA18647468 Valsartan										
Parameter	Standard Curve Samples									
Concentration (µg/mL)	0.02000	0.04000	0.08000	0.2000	0.6000	1.200	2.400	4.800	9.600	12.00
*Inter day Precision (%CV)	1.8	2.4	2.3	5.9	3.0	3.5	2.3	3.9	4.4	5.1
*Inter day Accuracy (%Actual)	97.0	103	105	102	105	102	103	96.3	95.2	92.1
Linearity (r ² value)	0.9940820 – 0.9986658									
Linearity Range (µg/mL)	0.02000 – 12.00									
Sensitivity/LOQ (µg/mL)	0.02000									
Bioequivalence Study No. BA18647468 Valsartan										
Parameter	Quality Control Samples									
Concentration (µg/mL)	LQC 0.06000		MQC-2 0.7200		MQC-1 4.200			HQC 9.000		
*Inter day Precision (%CV)	5.7		5.1		4.2			5.2		
*Inter day Accuracy (%Actual)	100		104		98.2			96.3		

Note: * = Results are reported as inter run.

Table 15 SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
(b)(4)		Sample Reanalysis and reporting criteria

Table 16 Composition of Non-Standard Breakfast Meal Used in Fed Bioequivalence Study-BA18647468

Standard FDA Meal Used?		☐ Yes ☒ No				
If No, then meal components and composition is listed in the table below						
Composition of Non-standard FDA Meal Used in Fed Bioequivalence Study						
Ingredients		Amount* (g)	Energy (kcal)	Protein (kcal)	Fat (kcal)	Carbohydrate (kcal)
Milk (Sterilised Flavoured)	Milk	250 mL	221.750	32.000	69.750	120.000
Chicken Dana	Chicken	70	120.036	63.336	56.700	0.000
	Refined Flour	20	69.072	8.288	1.368	59.416
	Oil	20 mL	180.000	0.000	180.000	0.000
Bread Butter	Bread	20	49.020	6.240	1.260	41.520
	Butter	10	72.200	0.200	72.000	0.000
Potato Chaat	Potato	40	27.116	2.464	0.828	23.824
	Oil	5 mL	45.000	0.000	45.000	0.000
Paneer	Paneer	15	38.713	11.316	19.953	7.444
	Oil	2 mL	18.000	0.000	18.000	0.000
Boiled Egg Masala	Egg	50	84.780	26.280	58.500	0.000
TOTAL			925.687	150.124	523.359	252.204
PERCENTAGE			NA	16.218	56.537	27.245

*Quantity of Raw Ingredients

4.4.2 SAS Output

As stated previously in the individual assessment sections for the fasting and fed studies, the assessor's SAS evaluation is currently pending.

NOTE TO DBI PROJECT MANAGER and REGULATORY PROJECT MANAGER (RPM): As per OGD Policy, a Citizen Petition (CP) is pending for this drug product which states the following:

CP # FDA-2019-P-1893, for ENTRESTO® (sacubitril/valsartan) tablet requests FDA to: (1) Require ANDAs that reference ENTRESTO to demonstrate API sameness; (2) Revise FDA's Draft Guidance document regarding sacubitril/valsartan oral tablets to recommend that API sameness be established by showing that the chemical structure of each active ingredient in the finished dosage form of a proposed generic is identical to the chemical structure of each active ingredient in the RLD, including all ionic bonds; (3) Further revise the Draft Guidance to include BE and PK requirements.

Actions: No Approval Actions (AP/TA) can be taken prior to contacting Policy Lead.

Citizen petition (FDA-2019-P-2869) for Multiple drug products containing valsartan, which requests FDA to: 1) review and significantly lower the acceptable intake/permitted daily exposure limit of DMF, as listed in the current FDA guidance Q3C – Tables and List, Guidance for Industry, from its current level of 8,800,000 nanograms to less than 1,000 nanograms (and potentially as low as 96 nanograms); 2) request a recall of identified lots of valsartan on the basis that, due to contamination with a probable human carcinogen, these drugs are adulterated under Section 501 of the FDCA (21 U.S.C. § 351) and misbranded under Section 502 of the FDCA (21 U.S.C. § 352); 3) conduct examinations and investigation under Section 702 (a) of the FDCA (21 U.S.C. § 372(a)) regarding these products, their manufacturing processes, and the manufacturer submissions made for FDA approval under 704 (a) of the FDCA (21 U.S.C. § 374(a)) and effect labeling revisions as needed

Actions: No Approval Actions (AP/TA) can be taken prior to contacting Policy Lead.

BIOEQUIVALENCE DEFICIENCY TO BE PROVIDED TO THE APPLICANT

ANDA: 213748

APPLICANT: MSN Laboratories Private Limited

DRUG PRODUCT: Sacubitril; Valsartan Tablets, 24 mg; 26 mg, 49 mg; 51 mg, and 97 mg; 103 mg

The Division of Bioequivalence I (DBI) has completed its review and has identified the following deficiency:

Per your submission dated 07/08/2019 [Module 5.3.1.2/Data Tabulation Data/Data Tabulation Dataset SDTM for both fasting and fed studies, files: ba18647469-conc-sacubitril.xpt, ba18647469-pk-sacubitril.xpt, ba18647469-conc-valsartan.xpt, and ba18647469-pk-valsartan.xpt (fasting study), and ba18647470-conc-sacubitril.xpt, ba18647470-pk-sacubitril.xpt, ba18647470-conc-valsartan.xpt, and ba18647470-pk-valsartan.xpt (fed study)], you provided concentration and pharmacokinetic (PK) datasets

for both analytes, sacubitril and valsartan, for your pivotal fasting (BA18647469) and fed (BA18647470) studies. Please provide updated versions of these datasets for both analytes for both pivotal studies after incorporating all available data for the subjects who were excluded from the statistical analyses. That is, please provide the revised concentration and PK datasets including the data for subjects # [REDACTED] for the pivotal fasting study, and subjects # [REDACTED] for the pivotal fed study. In addition, please provide the PK and statistical analysis results from the updated datasets.

Sincerely yours,

Utpal Munshi, Ph.D.
Acting Director, Division of Bioequivalence I
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

5 PRODUCTIVITY

Completed Assignment for 213748 ID: 40710

Reviewer: Manerikar, Archana

Date

Completed:

Verifier: ,

Date Verified:

Division: Division of Bioequivalence

Description: Review for Sacubitril; Valsartan Tablets, 24 mg; 26 mg, 49 mg; 51 mg, and 97 mg; 103 mg

Items:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Score</i>	<i>Subtotal</i>		
40710	7/8/2019	BIO	ANDA Original [1]	1	1	Edit	Delete
40710	7/8/2019	Parallel	Fasting Study [1]	1	1	Edit	Delete
40710	7/8/2019	Parallel	Fasting Study (Additional Analyte) [0.25]	0.25	0.25	Edit	Delete
40710	7/8/2019	Parallel	Fed Study [1]	1	1	Edit	Delete
40710	7/8/2019	Parallel	Fed Study (Additional Analyte) [0.25]	0.25	0.25	Edit	Delete
40710	7/8/2019	Parallel	Dissolution-Based Waiver (IR) (For all waiver strengths) [0.25]	0.25	0.25	Edit	Delete
40710	7/8/2019	Parallel	Pilot and Failed Full Extra Study for the Same Formulation as the Proposed Formulation (as defined in Guidance) [0.25]	0.5	0.5	Edit	Delete
				Total:	4.25		

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 213748

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS



ANDA 213748

**REQUEST FOR RECLASSIFICATION
REQUEST GRANTED**

MSN Pharmaceuticals Inc.
U.S. Agent for MSN Laboratories Private Limited
20 Duke Road
Piscataway, NJ 08854
Attention: Dr. Kondal Reddy Bairy
Associate Vice President

Dear Dr. Kondal Reddy Bairy:

This is in reference to your abbreviated new drug application (ANDA), submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act for Sacubitril and Valsartan Tablets, 24 mg/26 mg, 49 mg /51 mg and 97 mg/103 mg.

We also refer to your correspondence received on May 2, 2024, requesting to reclassify your facility based major complete response letter (CRL) amendment as a minor amendment.

The Office of Pharmaceutical Quality has reviewed your request to reclassify your facility based major CRL amendment as a minor amendment and your request has been granted.

The GDUFA goal date for review of this standard minor amendment is October 2, 2024.

If you have any questions, contact Gwendolyn Murphy, Regulatory Project Manager, at (240) 402 - 9624.

Sincerely,

{See appended electronic signature page}

Gwendolyn Murphy
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration



Gwendolyn
Murphy

Digitally signed by Gwendolyn Murphy

Date: 6/02/2024 09:04:56AM

GUID: 542af06d01243746ca2493dc5935bd01



ANDA 213748

AMENDMENT ACKNOWLEDGEMENT
Standard
Major

MSN Pharmaceuticals Inc.
U.S. Agent for MSN Laboratories Private Limited
20 Duke Road
Piscataway, NJ 08854
Attention: Dr. Kondal Reddy Bairy
Associate Vice President

Dear Dr. Kondal Reddy Bairy:

This is in reference to your amendment received on May 2, 2024, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Sacubitril and Valsartan Tablets, 24 mg/26 mg, 49 mg /51 mg and 97 mg/103 mg.

We acknowledge your request to reclassify your facility based major complete response letter (CRL) amendment as a minor amendment. Your request has been forwarded to the Office of Pharmaceutical Quality for review. This amendment is subject to the provisions of the Generic Drug User Fee Amendments of 2022 (GDUFA III). FDA has made an initial determination that this is a standard amendment.

The GDUFA goal date for providing our written response is July 1, 2024.

GDUFA provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the reference listed drug (RLD) that occur after the submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure your application stays up to date with the Agency's current recommendations on demonstrating bioequivalence reflected in relevant product specific guidances.

As described in FDA's Draft Guidance for Industry, *Cover Letter Attachments for Controlled Correspondences and ANDA Submissions*, FDA recommends that you include the appropriate attachment(s) along with the cover letter for your submission to help FDA ensure that your submission is properly triaged and assigned to the appropriate assessors. This will also ensure that submissions are effectively managed

by FDA and acted upon within the performance review goal dates set by the Generic Drug User Fee Amendments.

If you have any questions, contact Gwendolyn Murphy, Regulatory Project Manager, at (240) 402 - 9624.

Sincerely,

{See appended electronic signature page}

Gwendolyn Murphy
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration



Gwendolyn
Murphy

Digitally signed by Gwendolyn Murphy
Date: 5/02/2024 05:07:38PM
GUID: 542af06d01243746ca2493dc5935bd01



ANDA 213748

COMPLETE RESPONSE

MSN Pharmaceuticals Inc.
U.S. Agent for MSN Laboratories Private Limited
20 Duke Road
Piscataway, NJ 08854
Attention: Dr. Kondal Reddy Bairy
Associate Vice President

Dear Dr. Kondal Reddy Bairy:

This is in reference to your abbreviated new drug application (ANDA) received for review on July 8, 2019, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Sacubitril and Valsartan Tablets, 24 mg/26 mg, 49 mg /51 mg and 97 mg/103 mg.

We acknowledge receipt of the December 27, 2022 submission, which constituted a complete response to our May 2, 2022 action letter, and to any amendments thereafter.

We have completed our review of this ANDA, as amended, and have determined that we cannot approve this ANDA in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PHARMACEUTICAL QUALITY

Manufacturing

The Pharmaceutical Quality deficiencies have been classified as MAJOR because one or more facilities were found inadequate at the time of action due to inspectional deficiencies as noted in Appendix A, Section A(6)(a) of the Guidance for Industry, ANDA Submissions - Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). Note that after the deficiencies have been purportedly resolved, FDA must assess the resolution of the cited deficiencies during the next review cycle. This assessment, upon receipt of an amendment responding to this deficiency, in FDA's judgement, will require substantial expenditure of FDA resources.

(b)(4)

LABELING

Prior to final approval, the proposed labeling should be clear and precise (grammar, spelling, and formatting) for end users, and accurately reflect the Reference Listed Drug (RLD) information to comply with FDA policies, laws, regulations (i.e., 21 CFR 314.94(a)(8)), official compendia, and relevant guidance.

GENERAL COMMENTS

(b)(4)	
(b)(4)	Ensure your labeling is in accordance with the most recently approved labeling of the RLD.

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

DRUG SUBSTANCE/DRUG PRODUCT/BIPHARMACEUTICS/BIOEQUIVALENCE

There are no further questions for the above listed disciplines at this time. The comments provided in this communication are comprehensive as of the date the discipline review was completed. However, these comments are subject to revision if any scientific or regulatory division identifies additional concerns, as well as any concerns due to inspection results that may arise in the future. Additionally, the compliance status of each facility named in the application may be re-evaluated upon re-submission.

FDA publishes new and revised product-specific guidances describing the Agency's current recommendations on demonstrating bioequivalence and certain other approval

requirements. To ensure you are aware of FDA's recommendations for the most accurate, sensitive, and reproducible methodology to demonstrate bioequivalence (21 CFR 320.24(a)), please continue to monitor for the availability of new and revised product-specific guidances in the *Federal Register* and on the FDA Web site at the following address:

<https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm>.

POLICY

We note that on September 12, 2022, Novartis Pharmaceuticals Corporation (Novartis) submitted a citizen petition (Docket No. FDA-2022-P-2228) requesting, among other things, that FDA refrain from approving any ANDA relying on NDA 207620 for Entresto as the reference listed drug until after the expiration of the following patents 1) U.S. Patent Nos. 9,517,226; 9,937,143; and 11,135,192, each expiring on August 22, 2033, and each listed in the Orange Book with the patent use code "U-3084: (Treatment of Heart Failure With Preserved Ejection Fraction)" and (2) U.S. Patent No. 11,058,667 listed in the Orange Book, expiring May 9, 2036, and listed with the patent use code U-3170 (treating chronic heart failure with reduced ejection fraction in patients not taking an ace inhibitor or an ARB or previously taking low doses of these agents, by titrating up from half the usually recommended starting dose). In this complete response letter, we have included only comments that are unrelated to the citizen petition issues (FDA-2022-P-2228). Per Section XI, paragraph E of the GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2023-2027 ("GDUFA III Commitment Letter"), a response that addresses all other issues unrelated to the citizen petition is still considered a complete response. Since the citizen petition raises labeling issues that would delay only part of a complete response, we are including only comments unrelated to the pending citizen petition until a citizen response has been finalized. Additional changes to the proposed labeling of an ANDA for sacubitril and valsartan tablets may be required as the Agency continues to consider issues raised by this petition and Orange Book-listed patents.

We also note that on April 18, 2019, Novartis submitted a citizen petition to FDA (Docket No. FDA-2019-P-1893) requesting that FDA require ANDAs that reference ENTRESTO (sacubitril and valsartan) tablets to demonstrate active pharmaceutical ingredient (API) sameness based on the chemical structure of the sacubitril and valsartan active ingredients present in the finished dosage form; revise FDA's draft product-specific guidance (PSG) on sacubitril and valsartan oral tablets to recommend API sameness be established by showing that the chemical structure of each API in the finished dosage form of a proposed generic is identical to the chemical structure of each API in the RLD; and further revise the PSG to include other criteria.

The issues raised by these citizen petitions are currently under review by the Agency, and FDA has not made a final decision on the issues the petitions raise. The comments included in this communication reflect only our current thinking, and this communication

does not represent a final decision by the Agency on the issues raised in the pending citizen petitions.

OTHER

The resubmission to this CR letter will be considered to represent a **MAJOR AMENDMENT**, given that the deficiencies have been classified as **MAJOR**.

Prominently identify the submission with the following wording in bold, capital letters at the top of the first page of the submission. If your submission includes gratuitous information in addition to the category or categories below, clearly identify the type of information submitted immediately following the wording below:

**RESUBMISSION
MAJOR
COMPLETE RESPONSE AMENDMENT
MANUFACTURING/LABELING/POLICY**

Upon review of your amendment, FDA may identify information in the amendment that may require a change in classification and an adjustment to the goal date.

Within one year after the date of this letter, you are required to respond by taking one of the actions available under 21 CFR 314.110(b). If you do not take one of these actions, we may consider your lack of response as a request to withdraw the ANDA under 21 CFR 314.110(c)(1). You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter does not fulfill the requirements in 21 CFR 314.110(b)(1) and therefore will not be processed as a resubmission and will not start a new review cycle. Note that an amendment in response to a CRL classified by FDA as Minor that is submitted more than one year after the date FDA issued the CRL will be reclassified as a Major Amendment, except for ANDAs for products that are on the drug shortage list under section 506E of the FD&C Act (21 U.S.C. 356e), or are the subject of a response to a Public Health Emergency as declared by the Secretary of the U.S. Department of Health and Human Services under section 319 of the Public Health Service Act (PHS Act) (42 U.S.C. 247d), or are anticipated to be subject to the same criteria as apply to such a declaration, at the time of submission.

The drug product may not be marketed without final Agency approval under section 505(j) of the FD&C Act.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions¹ with respect to self-identification of facilities and payment of annual facility fees. ANDAs that identify at least one facility that is referenced in an approved ANDA are subject to the self-identification requirement and

to payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts.

All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self-identification or fee payment.

GDUFA provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to maximize the efficiency and utility of each assessment cycle, with the intent to reduce the number of assessment cycles for ANDAs and facilitate timely access to quality, affordable, safe, and effective generic medicines. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the RLD that occur after submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure you stay up to date with the Agency's current thinking on topics through guidances for industry, including product-specific guidances.

As described in the *Cover Letter Attachments for Controlled Correspondences and ANDA Submissions Draft Guidance for Industry*, FDA recommends that you include the appropriate attachment(s) along with the cover letter for your submission to help FDA ensure that your submission is properly triaged and assigned to the appropriate assessors. This will also ensure that submissions are effectively managed by FDA and acted upon with the performance review goal dates set by the Generic Drug User Fee Amendments.

If you have any questions, call Gwendolyn Murphy, Regulatory Project Manager, Division of Project Management, at (240) 402 - 9624.

Sincerely yours,

{See appended electronic signature page}

For Vincent Sansone, PharmD
CAPT United States Public Health Service
Director, Division of Project Management
Office of Regulatory Operations
Office of Generic Drugs

¹ Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).



David
Eng

Digitally signed by David Eng

Date: 3/22/2024 08:16:48AM

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ANDA 213748

AMENDMENT ACKNOWLEDGEMENT
Standard
Minor

MSN Pharmaceuticals Inc.
U.S. Agent for MSN Laboratories Private Limited
20 Duke Road
Piscataway, NJ 08854
Attention: Dr. Kondal Reddy Bairy
Associate Vice President

Dear Dr. Kondal Reddy Bairy:

This is in reference to your amendment received on July 6, 2023, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Sacubitril and Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg.

This amendment is subject to the provisions of the Generic Drug User Fee Amendments of 2022 (GDUFA III). FDA has made an initial determination that this is a standard minor amendment. The GDUFA goal date for review of this standard minor amendment is October 6, 2023. We also note that, consistent with the GDUFA III Commitment Letter, your information request/discipline review letter (IR/DRL) response extends the goal date for your ANDA.

GDUFA provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the reference listed drug (RLD) that occur after the submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure your application stays up to date with the Agency's current recommendations on demonstrating bioequivalence reflected in relevant product specific guidances.

As described in FDA's Draft Guidance for Industry, *Cover Letter Attachments for Controlled Correspondences and ANDA Submissions*, FDA recommends that you include the appropriate attachment(s) along with the cover letter for your submission to help FDA ensure that your submission is properly triaged and assigned to the appropriate assessors. This will also ensure that submissions are effectively managed by FDA and acted upon within the performance review goal dates set by the Generic Drug User Fee Amendments.

U.S. Food & Drug Administration
Silver Spring, MD 20993
www.fda.gov

If you have any questions, contact Gwendolyn Murphy, Regulatory Project Manager, at (240) 402 - 9624.

Sincerely,

{See appended electronic signature page}

Gwendolyn Murphy
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration



Gwendolyn
Murphy



Digitally signed by Gwendolyn Murphy

Date: 7/06/2023 12:26:43PM

GUID: 542af06d01243746ca2493dc5935bd01



ANDA 213748

**INFORMATION REQUEST
QUALITY**

MSN Pharmaceuticals Inc.
U.S. Agent for MSN Laboratories Private Limited
20 Duke Road
Piscataway, NJ 08854-3714
Attention: Dr. Kondal Reddy Bairy

Dear Dr. Kondal Reddy Bairy:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on July 8, 2019, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Sacubitril and Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg.

We are reviewing the Quality section of your submission and request the following additional information/clarification and/or have the following comments:

QUALITY

A. Drug Product

1.

(b)(4)

We request a complete written response, no later than July 6, 2023 in order to continue our evaluation of your ANDA. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an amendment and assign an appropriate goal date for that amendment. If you are responding to a late cycle information request¹, the goal date may be extended based upon the major or minor deficiencies included upon receipt of the response. The goal date assigned to the amendment may extend the review goal date for your current submission.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

**INFORMATION REQUEST
QUALITY
MINOR**

If you do not submit a complete written response by July 6, 2023, the listed information requests may be incorporated in a discipline review letter or complete response letter.

As described in FDA's draft guidance for industry *Cover Letter Attachments for Controlled Correspondences and ANDA Submissions*, FDA recommends that you include the appropriate attachment(s) along with the cover letter for your submission to help FDA ensure that your submission is properly triaged and assigned to the appropriate assessors. This will also ensure that submissions are effectively managed by FDA and acted upon within the performance review goal dates set by the Generic Drug User Fee Amendments.

If you have any questions, please contact Candice Cottle-Delisle, Regulatory Business Process Manager, at candice.cottle-delisle@fda.hhs.gov or (240) 402 - 0084.

Sincerely,

{See appended electronic signature page}

Candice Cottle-Delisle
Regulatory Business Process Manager
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

¹ Late cycle defined as IRs or DRLs issued after the mid-cycle of an original ANDA or less than 90 days from the goal date for any ANDA amendment.



Candice
Cottle-Delisle



Digitally signed by Candice Cottle-Delisle

Date: 6/29/2023 02:28:05PM

GUID: 556484f0002937bc2b3a29c7b0f22580



ANDA 213748

AMENDMENT ACKNOWLEDGEMENT
Standard
Major

MSN Pharmaceuticals Inc.
U.S. Agent for MSN Laboratories Private Limited
20 Duke Road
Piscataway, NJ 08854-3714
Attention: Kondal Reddy Bairy

Dear Kondal Reddy Bairy:

This is in reference to your amendment received on December 27, 2022, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Sacubitril and Valsartan Tablets, 24 mg/26 mg, 49 mg /51 mg, and 97 mg/103 mg.

This amendment is subject to the provisions of the Generic Drug User Fee Amendments of 2022 (GDUFA III). FDA has made an initial determination that this is a standard major amendment. If FDA determines that an inspection is not required to validate the information contained in this standard major amendment, the GDUFA goal date for review of this standard major amendment is August 27, 2023. If this standard major amendment requires an inspection, the goal date for review of this standard major amendment is October 27, 2023. Two possible goal dates are provided because FDA is unable to determine if an amendment requires an inspection at the time of submission. FDA will make this determination during the assessment of the amendment. For more information, see FDA's guidance for industry, *ANDA Submissions - Amendments to Abbreviated New Drug Applications Under GDUFA*.

GDUFA provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the reference listed drug (RLD) that occur after the submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure your application stays up to date with the Agency's current recommendations on demonstrating bioequivalence reflected in relevant product specific guidances.

As described in FDA's Draft Guidance for Industry, Cover Letter Attachments for Controlled Correspondences and ANDA Submissions, FDA recommends that you include the appropriate attachment(s) along with the cover letter for your submission to

help FDA ensure that your submission is properly triaged and assigned to the appropriate assessors. This will also ensure that submissions are effectively managed by FDA and acted upon within the performance review goal dates set by the Generic Drug User Fee Amendments.

If you have any questions, please contact Gwendolyn Murphy, Regulatory Project Manager, at (240) 402 - 9624.

Sincerely,

{See appended electronic signature page}

Gwendolyn Murphy
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration



Meenu
Sharma

Digitally signed by Meenu Sharma
Date: 12/28/2022 12:29:36PM
GUID: 5d66aea1000bf56fa5e0d77e3fc8b287



ANDA 213748

COMPLETE RESPONSE

MSN Pharmaceuticals Inc.
U.S. Agent for MSN Laboratories Private Limited
20 Duke Road
Piscataway, NJ 08854
Attention: Dr. Kondal Reddy Bairy
Senior Director

Dear Dr. Kondal Reddy Bairy:

This is in reference to your abbreviated new drug application (ANDA) received for review on July 8, 2019, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Sacubitril and Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg.

We acknowledge receipt of the February 9, 2022 submission, which constituted a complete response to our April 30, 2021 action letter, and to any amendments thereafter.

We have completed our review of this ANDA, as amended, and have determined that we cannot approve this ANDA in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PHARMACEUTICAL QUALITY

The Pharmaceutical Quality deficiencies have been classified as MAJOR because new analytical methods are needed to assure product quality as noted in Appendix A, Section A(2)(i) of the guidance for industry ANDA Submissions – Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). Upon receipt, in FDA's judgement, the review of these methods will require substantial expenditure of FDA resources.

Drug Substance

(b)(4)

(b)(4)

Drug Product

(b)(4)

LABELING

1. GENERAL COMMENTS

We note that on December 1, 2021, Novartis Pharmaceuticals Corporation (Novartis) submitted a citizen petition to FDA (Docket No. FDA-2021-P-1286) requesting that FDA not approve any ANDA referencing NDA 207620 ENTRESTO (sacubitril and valsartan) oral tablets until the expiration of the following patents and exclusivities: 3-year exclusivity period covering the labeling changes approved in the February 2021 supplement, including any ANDA that seeks to add language to, or otherwise revise, the existing indication statement in order to omit the exclusivity-protected use; the expiration of the HFpEF Patents if that ANDA contains a section viii statement to these patents and seeks to omit the patent-protected use in HFpEF patients; and the expiration of the '667 Patent if that ANDA contains a section viii statement and seeks to omit the modified dosing regimen for HFpEF patients not taking an ACE inhibitor or ARB, or who were previously taking low doses of these agents. We also note that on April 18, 2019, Novartis submitted a citizen petition to FDA (Docket No. FDA-2019-P-1893) requesting that FDA require ANDAs that reference ENTRESTO (sacubitril and valsartan) tablets to demonstrate active pharmaceutical ingredient (API) sameness based on the chemical structure of the sacubitril and valsartan active ingredients present in the finished dosage form; revise FDA's draft product-specific guidance (PSG) on sacubitril and valsartan oral tablets to recommend API sameness be established by showing that the chemical structure of each API in the finished dosage form of a proposed generic is identical to the chemical structure of each API in the RLD; and further revise the PSG to include other criteria. The issues raised by these petitions are currently under review by the Agency, and FDA has not made a final decision on the issues the petition raises. The comments included in this communication reflect only our current thinking, and

this communication does not represent a final decision by the Agency on the issues raised in the pending citizen petitions.

2. PRESCRIBING INFORMATION

a. HIGHLIGHTS:

- i. Indications and Usage: Revise to read, "to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure and reduced ejection fraction (1.1).".
- ii. Dosage and Administration: Include the bullet point, "Reduce starting dose to half the usually recommended starting dosage for:" for clarity.

b. INDICATIONS AND USAGE:

- i. Revise to read, "Sacubitril and valsartan is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure and reduced ejection fraction.".
- ii. Retain the sentence, "LVEF is a variable measure, so use clinical judgment in deciding whom to treat [see Clinical Studies (14.1)].".

c.

(b)(4)

d.

(b)(4)

3. PATIENT INFORMATION LEAFLET

At the end of the list of inactive ingredients, include, "Prepared sacubitril and valsartan oral suspension also contains Ora-Sweet SF® and Ora-Plus.®". Additionally, include the disclaimer, "All brand names listed are the registered trademarks of their respective owners. ".

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated

and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book (OB), and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

MANUFACTURING/BIOPHARMACEUTICS/BIOEQUIVALENCE

There are no further questions for the above listed disciplines at this time. The comments provided in this communication are comprehensive as of the date the discipline review was completed. However, these comments are subject to revision if any scientific or regulatory division identifies additional concerns, as well as any concerns due to inspection results that may arise in the future. Additionally, the compliance status of each facility named in the application may be re-evaluated upon re-submission.

FDA publishes new and revised product-specific guidances describing the Agency's current recommendations on demonstrating bioequivalence and certain other approval requirements. To ensure you are aware of FDA's recommendations for the most accurate, sensitive, and reproducible methodology to demonstrate bioequivalence (21 CFR 320.24(a)), please continue to monitor for the availability of new and revised product-specific guidances in the *Federal Register* and on the FDA Web site at the following address:

<https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm>.

OTHER

The resubmission to this CR letter will be considered to represent a **MAJOR AMENDMENT**, given that the deficiencies have been classified as **MAJOR**.

Prominently identify the submission with the following wording in bold, capital letters at the top of the first page of the submission. If your submission includes gratuitous information in addition to the category or categories below, clearly identify the type of information submitted immediately following the wording below:

**RESUBMISSION
MAJOR
COMPLETE RESPONSE AMENDMENT
DRUG SUBSTANCE/DRUG PRODUCT/LABELING**

U.S. Food & Drug Administration
Silver Spring, MD 20993
www.fda.gov

Upon review of your amendment, FDA may identify information in the amendment that may require a change in classification and an adjustment to the goal date.

Within one year after the date of this letter, you are required to respond by taking one of the actions available under 21 CFR 314.110(b). If you do not take one of these actions, we may consider your lack of response as a request to withdraw the ANDA under 21 CFR 314.110(c)(1). You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter does not fulfill the requirements in 21 CFR 314.110(b)(1) and therefore will not be processed as a resubmission and will not start a new review cycle.

The drug product may not be marketed without final Agency approval under section 505(j) of the FD&C Act.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions¹ with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self-identification or fee payment.

GDUFA II provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including by fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the RLD that occur after submission

of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure you stay up to date with the Agency's current thinking on topics through guidances for industry, including product-specific guidances.

If you have any questions, call Gwendolyn Murphy, Regulatory Project Manager, Division of Project Management, at (240) 402 - 9624.

Sincerely yours,

{See appended electronic signature page}

For Denise P. Toyer McKan, PharmD
Director, Division of Project Management
Office of Regulatory Operations
Office of Generic Drugs

¹ Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).



Mandy
Kwong



Digitally signed by Mandy Kwong

Date: 5/02/2022 03:57:36PM

GUID: 529372550000cc96a0a98e57d06862e5



ANDA 213748

INFORMATION REQUEST

MSN Pharmaceuticals Inc.
U.S. Agent for MSN Laboratories Private Limited
20 Duke Road
Piscataway, NJ 08854-3714
Attention: Dr.Kondal Reddy Bairy

Dear Sir or Madam:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on July 8, 2019, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Sacubitril and Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg.

We are reviewing the Quality section of your submission and have the following comments and information requests:

A. Manufacturing

Process

1.

(b)(4)

We request a prompt written response, no later than February 22, 2022 in order to continue our evaluation of your ANDA. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an amendment and assign an appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

U.S. Food & Drug Administration
Silver Spring, MD 20993
www.fda.gov

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

**INFORMATION REQUEST
QUALITY**

If you have any questions, please contact Candice Cottle-Delisle, Regulatory Business Process Manager, at candice.cottle-delisle@fda.hhs.gov or (240) 402 - 0084.

Sincerely,

{See appended electronic signature page}

Candice Cottle-Delisle
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Candice
Cottle-Delisle



Digitally signed by Candice Cottle-Delisle

Date: 2/18/2022 10:54:37PM

GUID: 556484f0002937bc2b3a29c7b0f22580



ANDA 213748

AMENDMENT ACKNOWLEDGEMENT
Standard
Minor

MSN Pharmaceuticals Inc.
U.S. Agent for MSN Laboratories Private Limited
20 Duke Road
Piscataway, NJ 08854
Attention: Dr. Kondal Reddy Bairy
Senior Director

Dear Dr. Kondal Reddy Bairy:

This is in reference to your amendment received on February 9, 2022, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Sacubitril and Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg.

This amendment is subject to the provisions of the Generic Drug User Fee Amendments of 2017 (GDUFA II). FDA has made an initial determination that this is a standard minor amendment. The GDUFA goal date for review of this standard minor amendment is May 8, 2022.

GDUFA II provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the RLD that occur after the submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure your application stays up to date with the Agency's current recommendations on demonstrating bioequivalence reflected in relevant product specific guidances.

If you have any questions, contact Gwendolyn Murphy, Regulatory Project Manager, at (240) 402 - 9624.

Sincerely,

{See appended electronic signature page}

Gwendolyn Murphy
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration



Gwendolyn
Murphy

Digitally signed by Gwendolyn Murphy

Date: 2/10/2022 04:16:40PM

GUID: 542af06d01243746ca2493dc5935bd01



ANDA 213748

AMENDMENT ACKNOWLEDGEMENT
Standard
Minor

MSN Pharmaceuticals Inc.
U.S. Agent for MSN Laboratories Private Limited
20 Duke Road
Piscataway, NJ 08854
Attention: Dr.Kondal Reddy Bairy
Associate Director

Dear Sir:

This is in reference to your amendment received on March 17, 2021, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Sacubitril and Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg.

This amendment is subject to the provisions of the Generic Drug User Fee Amendments of 2017 (GDUFA II). FDA has made an initial determination that this is a standard minor amendment. The GDUFA goal date for review of this standard minor amendment is June 16, 2021.

GDUFA II provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the RLD that occur after the submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure your application stays up to date with the Agency's current recommendations on demonstrating bioequivalence reflected in relevant product specific guidances.

If you have any questions, contact Gwendolyn Murphy, Regulatory Project Manager, at (240) 402 - 9624.

Sincerely,

{See appended electronic signature page}

Gwendolyn Murphy
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration



Gwendolyn
Murphy



Digitally signed by Gwendolyn Murphy

Date: 3/18/2021 05:11:14PM

GUID: 542af06d01243746ca2493dc5935bd01



ANDA 213748

COMPLETE RESPONSE

MSN Pharmaceuticals Inc.
U.S. Agent for MSN Laboratories Private Limited
20 Duke Road
Piscataway, NJ 08854
Attention: Dr. Kondal Reddy Bairy
Associate Director

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) received for review on July 8, 2019, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Sacubitril and Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg.

We acknowledge receipt of the August 19, 2020 submission, which constituted a complete response to our June 8, 2020 action letter, and to any amendments thereafter.

We have completed our review of this ANDA, as amended, and have determined that we cannot approve this ANDA in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PHARMACEUTICAL QUALITY

Drug Substance

1.

(b)(4)

Drug Product

2.

(b)(4)

(b)(4)

Process

3.

(b)(4)

LABELING

GENERAL COMMENT

(b)(4)

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

BIOPHARMACEUTICS/FACILITY INSPECTION/BIOEQUIVALENCE

There are no further questions for the above listed disciplines at this time. The comments provided in this communication are comprehensive as of the date the discipline review was completed. However, these comments are subject to revision if any scientific or regulatory division identifies additional concerns, as well as any concerns due to inspection results that may arise in the future. Additionally, the compliance status of each facility named in the application may be re-evaluated upon re-submission.

FDA publishes new and revised product-specific guidances describing the Agency's current recommendations on demonstrating bioequivalence and certain other approval requirements. To ensure you are aware of FDA's recommendations for the most accurate, sensitive, and reproducible methodology to demonstrate bioequivalence (21 CFR 320.24(a)), please continue to monitor for the availability of new and revised product-specific guidances in the *Federal Register* and on the FDA Web site at the following address:

<https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm>.

OTHER

The resubmission to this CR letter will be considered to represent a **MINOR AMENDMENT**, given that the deficiencies have been classified as **MINOR**.

Provided that the amendment contains no additional information that requires a substantial expenditure of resources to review, prominently identify the submission with the following wording in bold, capital letters at the top of the first page of the submission. If your submission includes gratuitous information in addition to the category or categories below, clearly identify the type of information submitted immediately following the wording below:

**RESUBMISSION
MINOR
COMPLETE RESPONSE AMENDMENT
DRUG SUBSTANCE/DRUG PRODUCT/PROCESS/LABELING**

Upon review of your amendment, FDA may identify information in the amendment that may require a change in classification and an adjustment to the goal date.

Within one year after the date of this letter, you are required to respond by taking one of the actions available under 21 CFR 314.110(b). If you do not take one of these actions,

U.S. Food & Drug Administration
Silver Spring, MD 20993
www.fda.gov

we may consider your lack of response as a request to withdraw the ANDA under 21 CFR 314.110(c)(1). You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter does not fulfill the requirements in 21 CFR 314.110(b)(1) and therefore will not be processed as a resubmission and will not start a new review cycle.

The drug product may not be marketed without final Agency approval under section 505(j) of the FD&C Act.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions¹ with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self-identification or fee payment.

GDUFA II provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including by fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the RLD that occur after submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure you stay up to date with the Agency's current thinking on topics through guidances for industry, including product-specific guidances.

If you have any questions, call Gwendolyn Murphy, Regulatory Project Manager, Division of Project Management, at (240) 402 - 9624.

Sincerely yours,

{See appended electronic signature page}

For Denise P. Toyer McKan, PharmD
Director, Division of Project Management
Office of Regulatory Operations
Office of Generic Drugs

¹ Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).



Mandy
Kwong

Digitally signed by Mandy Kwong

Date: 4/30/2021 11:31:23AM

GUID: 529372550000cc96a0a98e57d06862e5



ANDA 213748

AMENDMENT ACKNOWLEDGEMENT
Standard
Major

MSN Pharmaceuticals Inc.
U.S. Agent for MSN Laboratories Private Limited
20 Duke Road
Piscataway, NJ 08854
Attention: Dr. Kondal Reddy Bairy
Associate Director

Dear Sir:

This is in reference to your amendment received on August 19, 2020, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Sacubitril and Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg.

This amendment is subject to the provisions of the Generic Drug User Fee Amendments of 2017 (GDUFA II). FDA has made an initial determination that this is a standard major amendment. If FDA determines that an inspection is not required to validate the information contained in this standard major amendment, the GDUFA goal date for review of this standard major amendment is April 18, 2021. If this standard major amendment requires an inspection, the goal date for review of this standard major amendment is June 18, 2021. Two possible goal dates are provided because FDA is unable to determine if an amendment requires an inspection at the time of submission. FDA will make this determination during the assessment of the amendment. For information, see FDA's guidance for industry, *ANDA Submissions - Amendments to Abbreviated New Drug Applications Under GDUFA*.

GDUFA II provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the RLD that occur after the submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure your application stays up to date with the Agency's current recommendations on demonstrating bioequivalence reflected in relevant product specific guidances.

If you have any questions, contact Gwendolyn Murphy, Regulatory Project Manager, at (240) 402-9624.

Sincerely,

{See appended electronic signature page}

For Gwendolyn Murphy
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration



Dawn
Kimble-Vance

Digitally signed by Dawn Kimble-Vance
Date: 8/19/2020 08:59:29PM
GUID: 5463e4f2002198f6be78c50124038c96



ANDA 213748

COMPLETE RESPONSE

MSN Pharmaceuticals Inc.
U.S. Agent for MSN Laboratories Private Limited
20 Duke Road
Piscataway, NJ 08854
Attention: Dr. Kondal Reddy Bairy
Associate Director

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) received for review on July 8, 2019, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Sacubitril and Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg.

Reference is also made to any amendments submitted prior to the issuance of this letter.

We have completed our review of this ANDA, as amended, and have determined that we cannot approve this ANDA in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PHARMACEUTICAL QUALITY

Drug Substance

1.

(b)(4)

Drug Product

2.

(b)(4)

3.

(b)(4)

4.

Process

5.

(b)(4)

Biopharmaceutics

6.

(b)(4)

Update your drug product release and stability specifications accordingly. In addition, please be advised, that all proposed exhibit batches are expected to meet these revised dissolution specifications in your stability program through your proposed expiry period. If dissolution failures are observed on stability, these should be described. Discuss any corrective actions to avert such dissolution failures and provide data from a new batch to demonstrate correction of the issue, if needed.

Facility Inspection

(b)(4)

receipt, in FDA's judgement, the evaluation of new facilities added in an amendment and any additional inspections will require substantial expenditure of FDA resources.

7.

(b)(4)

BIOEQUIVALENCE/LABELING

There are no further questions for the above listed disciplines at this time. The comments provided in this communication are comprehensive as of the date the discipline review was completed. However, these comments are subject to revision if any scientific or regulatory division identifies additional concerns, as well as any concerns due to inspection results that may arise in the future. Additionally, the compliance status of each facility named in the application may be re-evaluated upon re-submission.

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OTHER

The resubmission to this CR letter will be considered to represent a **MAJOR AMENDMENT**, given that the deficiencies have been classified as **MAJOR**.

Prominently identify the submission with the following wording in bold, capital letters at the top of the first page of the submission:

**RESUBMISSION
MAJOR
COMPLETE RESPONSE AMENDMENT
DRUG SUBSTANCE/DRUG PRODUCT/PROCESS/
BIOPHARMACEUTICS/FACILITY INSPECTION**

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Within one year after the date of this letter, you are required to respond by taking one of the actions available under 21 CFR 314.110(b). If you do not take one of these actions, we may consider your lack of response as a request to withdraw the ANDA under 21 CFR 314.110(c)(1). You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter does not fulfill the requirements in 21 CFR 314.110(b)(1) and therefore will not be processed as a resubmission and will not start a new review cycle.

The drug product may not be marketed without final Agency approval under section 505(j) of the FD&C Act.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions¹ with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self-identification or fee payment.

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If you have any questions, call Gwendolyn Murphy, Regulatory Project Manager, Division of Project Management, at (240) 402 - 9624.

Sincerely yours,

{See appended electronic signature page}

For Denise P. Toyer McKan, PharmD
Director, Division of Project Management
Office of Regulatory Operations
Office of Generic Drugs

¹ Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).



Mandy
Kwong

Digitally signed by Mandy Kwong

Date: 6/08/2020 01:33:42PM

GUID: 529372550000cc96a0a98e57d06862e5



ANDA 213748

AMENDMENT ACKNOWLEDGEMENT

**Priority
Minor**

MSN Pharmaceuticals Inc.
U.S. Agent for MSN Laboratories Private Limited
20 Duke Road
Piscataway, NJ 08854
Attention: Dr. Kondal Reddy Bairy
Associate Director

Dear Sir:

This is in reference to your amendment received on March 23, 2020, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Sacubitril and Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg.

This amendment is subject to the provisions of the Generic Drug User Fee Amendments of 2017 (GDUFA II). FDA has made an initial determination that this is a minor amendment and it meets the criteria for a priority review per the Center for Drug Evaluation and Research's Manual of Policies and Procedures 5240.3, *Prioritization of the Review of Original ANDAs, Amendments, and Supplements*. The GDUFA goal date for review of this priority minor amendment is June 22, 2020.

GDUFA II provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the RLD that occur after the submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure your application stays up to date with the Agency's current recommendations on demonstrating bioequivalence reflected in relevant product specific guidances.

If you have any questions, contact Gwendolyn Murphy, Regulatory Project Manager, at (240) 402 - 9624.

Sincerely,

{See appended electronic signature page}

Gwendolyn Murphy
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration



Gwendolyn
Murphy

Digitally signed by Gwendolyn Murphy
Date: 3/24/2020 03:02:41PM
GUID: 542af06d01243746ca2493dc5935bd01



GENERAL ADVICE

MSN Laboratories Private Limited
Attn: Kondal Reddy Bairy
20 Duke Rd
Piscataway, NJ 08854-3714

Dear Kondal Reddy Bairy:

This letter is to update applicants with an approved or pending application for an

(b)(4)

Reference is made to FDA's [General Advice Letter](#)¹ issued in March 2019, which detailed FDA's understanding at that time of the known root causes of

(b)(4)

(b)(4)

FDA expects that, when feasible, manufacturers of APIs and drug products should take reasonable steps

(b)(4)

(b)(4)

(b)(4)

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IT IS NOT REASONABLE TO SEGREGATE MEANINGFUL PORTIONS OF THE RECORD FOR RELEASE.

INFORMATION HAS BEEN WITHHELD IN ITS ENTIRETY IN ACCORDANCE WITH THE FOLLOWING EXEMPTIONS(S):

(b) (4)

5 U.S.C. 552 (b) (4) - trade secrets and commercial or financial information obtained from a person and privileged or confidential.

Sincerely,

{See appended electronic signature page}

Vilayat A. Sayeed, Ph.D.
Director
Division of Immediate Release Products I
Office of Lifecycle Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Vilayat
Sayeed

Digitally signed by Vilayat Sayeed

Date: 2/14/2020 12:39:35PM

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Comments: signed off



ANDA 213748

**DISCIPLINE REVIEW LETTER
QUALITY**

MSN Pharmaceuticals Inc
U.S. Agent for Msn Laboratories Private Limited
20 Duke Road
Piscataway, NJ 08854
Attention: Dr. Kondal Bairy

Dear Dr. Kondal Bairy:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on July 8, 2019, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Sacubitril and Valsartan Tablets, 24 mg / 26 mg, 49 mg / 51 mg, 97 mg / 103 mg.

The following possible deficiencies have been identified by the Office of Pharmaceutical Quality:

A. Drug Substance:

1.

2.

(b)(4)

B. Drug Product:

1.

(b)(4)

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(b) (4)

5 U.S.C. 552 (b) (4) - trade secrets and commercial or financial information obtained from a person and privileged or confidential.

(b)(4)

If you would like to respond to these possible deficiencies before the end of this review cycle, we request a complete written response to this discipline review letter (DRL) no later than January 27, 2020. If you submit a written response during this review cycle, depending on the timing and/or the information contained in your response, we may not be able to consider your response before taking action on your application. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

**DISCIPLINE REVIEW LETTER
QUALITY**

Please note that we are providing these preliminary thoughts on possible deficiencies to you before a complete review of your entire application. As contemplated in the Generic Drug User Fee Amendments of 2017 (GDUFA II) Commitment Letter¹, these possible deficiencies do not reflect a complete review of your application and should not be construed as such. In addition, these possible deficiencies do not necessarily reflect input from supervisory levels. You should be aware that these deficiencies may be

modified or additional deficiencies may be identified as we complete our review of your entire application.

Deficiencies addressed by applicants in a response to a DRL may appear in a Complete Response Letter (CRL) if FDA's review of the response has been deferred or if FDA has outstanding concerns after review of the response. The CRL will include all deficiencies that must be satisfactorily addressed before the ANDA can be approved.

If the applicant receives a CRL, but has already responded to some (or all) identified deficiencies in a DRL response, the applicant does not need to re-submit previously submitted information in a CRL amendment. However, the applicant should still submit a CRL amendment and should clearly identify the previously provided DRL response that renders its CRL amendment complete.

Additionally, please take note of the following if you choose to respond to these possible deficiencies before the end of this review cycle:

1. FDA will strive to review your response during the review cycle in which it is received if such review can be completed during such review cycle. However, if the Agency determines that it cannot review the response before a goal date or if a complete response letter is otherwise ready to be issued, the review of your response may be deferred. When FDA defers review of your response, it will be reviewed during the next review cycle for the application.
2. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an amendment and assign an appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

If you have any questions, please contact Helina Zenebe, PharmD, Regulatory Business Process Manager, at helina.zenebe@fda.hhs.gov or (240) 402 - 4033.

Sincerely,

{See appended electronic signature page}

Helina Zenebe, PharmD
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

- ¹ GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (available at: <https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf>).



Helina
Zenebe

Digitally signed by Helina Zenebe

Date: 12/23/2019 06:36:52PM

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