

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
ANDA 213676

Name: Sacubitril and Valsartan Tablet, 24mg/25mg, 49mg/51mg,
and 97mg/103mg.

Sponsor: Laurus Labs Limited

Approval Date: May 28, 2024

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APPLICATION NUMBER:

ANDA 213676

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APPLICATION NUMBER:

ANDA 213676

APPROVAL LETTER



ANDA 213676

ANDA APPROVAL

Laurus Generics Inc.
U.S. Agent for Laurus Labs Limited
400 Connell Drive, Suite 5200
Berkeley Heights, NJ 07922
Attention: Sharath Koripally
Senior Director - RA, QA & PV

Dear Sharath Koripally:

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 December 20, 2022, 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 Corp. (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 each of the patents¹, 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 Laurus Labs Limited (Laurus) 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 Laurus for infringement of the '659, '938 and '134 patents in the United States District Court for the District of Delaware [Novartis Pharmaceuticals Corporation v. Alkem Laboratories Ltd., Aurobindo Pharma USA Inc., Aurobindo Pharma Ltd., Biocon Pharma Limited, Biocon Limited, Biocon Pharma, Inc., Crystal Pharmaceutical (Suzhou) Co., Ltd., Laurus Labs Limited, Laurus Generics Inc., Teva Pharmaceuticals USA, Inc., Torrent Pharma Inc., Torrent Pharmaceuticals Ltd., Civil Action No. 19-01979]. 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 180-day generic drug exclusivity, we note that Laurus 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, Laurus 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 Laurus 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 Laurus' 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 Laurus 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 Laurus 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

¹ The Agency notes that the '226, '143, '667 and '192 patents were submitted to the Agency after submission of your ANDA. Litigation, if any, with respect to these patents would not create a statutory stay of approval.



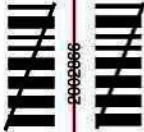
John
Ibrahim

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
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LABELING



HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all 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

See full prescribing information for complete boxed warning.

- When pregnancy is detected, discontinue sacubitril and valsartan as soon as possible. (5.1)
- Drugs 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 neprilisin inhibitor, and valsartan, an angiotensin II receptor blocker, and is indicated:

- 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. (1.1)
- for the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older. Sacubitril and valsartan tablets reduce NT-proBNP and are expected to improve cardiovascular outcomes. (1.2)

DOSAGE 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 doses 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, titrations, preparation and administration instructions. (2.3, 2.4)
- Reduce starting dose to half the usually recommended starting dosage for:

- patients not currently taking an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) or previously taking a low dose of these agents. (2.6)
- patients with severe renal impairment. (2.7)
- patients with moderate hepatic impairment. (2.8)

DOSAGE FORMS AND STRENGTHS

- Film-coated tablets: 24/26 mg; 49/51 mg; 97/103 mg (3)

CONTRAINDICATIONS

- Hypersensitivity to any component. (4)
- History of angioedema related to previous ACEi or ARB therapy. (4)
- Concomitant use with ACE inhibitors. (4, 7.1)
- Concomitant use with aliskiren in patients with diabetes. (4, 7.1)

WARNINGS AND PRECAUTIONS

- Observe for signs and symptoms of angioedema and hypotension. (5.2, 5.3)
- Monitor renal function and potassium in susceptible patients. (5.4, 5.5)

ADVERSE REACTIONS

Adverse reactions occurring greater than or equal to 5% are hypotension, hyperkalemia, cough, dizziness, and renal failure. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Laurus Generics Inc. at 1-833-3-LAURUS (1-833-352-8787) or FDA at 1-800-(FDA-1088) or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Avoid concomitant use with aliskiren in patients with estimated glomerular filtration rate (eGFR) less than 60. (7.1)
- Potassium-sparing diuretics: May lead to increased serum potassium. (7.2)
- Nonsteroidal Anti-Inflammatory Drugs (NSAIDs): May lead to increased risk of renal impairment. (7.3)
- Lithium: Increased risk of lithium toxicity. (7.4)

USE IN SPECIFIC POPULATIONS

- Lactation: Breastfeeding not recommended. (8.2)
- Severe Hepatic Impairment: Use not recommended. (2.8, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 5/2024

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FULL PRESCRIBING INFORMATION

WARNING: FETAL TOXICITY

- When pregnancy is detected, discontinue sacubitril and valsartan as soon as possible. (5.1)
- Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus. (5.1)

1 INDICATIONS AND USAGE

1.1 Adult Heart Failure

Sacubitril and valsartan tablets are indicated 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.

the dose to follow the recommended dose escalation thereafter [see Dosage and Administration (2.2, 2.3)].

Note: Initiate pediatric patients weighing 40 to 50 kg who meet this criterion at 0.8 mg/kg twice daily using the oral suspension [see Dosage and Administration (2.3, 2.4)]. No starting dose adjustment is needed for mild hepatic impairment. Use in patients with severe hepatic impairment is not recommended.

3 DOSAGE FORMS AND STRENGTHS

Sacubitril and valsartan tablets are supplied in the following strengths:

Sacubitril and valsartan tablets 24/26 mg, (sacubitril 24 mg and valsartan 26 mg) are violet white color, oval shaped, biconvex film-coated tablets debossed with "S5" on one side and plain on the

valsartan tablets 49/51 mg, (sacubitril 49 mg and valsartan 51 mg) are pale yellow

PATIENT INFORMATION
Sacubitril and Valsartan
(sak-UE-bi-tril and val-SAR-tan)
Tablets, for oral use

What is the most important information I should know about sacubitril and valsartan tablets?

Sacubitril and valsartan tablets can harm or cause death to your unborn baby. Talk to your doctor about other ways to treat heart failure if you plan to become pregnant. Tell your doctor right away if you become pregnant during treatment with sacubitril and valsartan tablets.

What are sacubitril and valsartan tablets?

Sacubitril and valsartan tablets are a prescription medicine used to treat:

- adults with long-lasting (chronic) heart failure to help reduce the risk of death and hospitalization. Sacubitril and valsartan tablet works better when the heart cannot pump a normal amount of blood to the body.
- certain children 1 year of age and older who have symptomatic heart failure.

It is not known if sacubitril and valsartan tablets are safe and effective in children under 1 year of age.

Do not take sacubitril and valsartan tablets if you:

- are allergic to any of the ingredients in sacubitril and valsartan tablets. See the end of this Patient Information leaflet for a complete list of ingredients in sacubitril and valsartan tablets.
- have had an allergic reaction, including swelling of your face, lips, tongue, throat, or trouble breathing while taking a type of medicine called an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB).
- take an ACE inhibitor medicine. **Do not take sacubitril and valsartan tablets for at least 36 hours before or after you take an ACE inhibitor medicine.** Talk with your doctor or pharmacist before taking sacubitril and valsartan tablets if you are not sure if you take an ACE inhibitor medicine.
- have diabetes and take a medicine that contains aliskiren.

Before taking sacubitril and valsartan tablets, tell your doctor about all of your medical conditions, including if you:

- have a history of hereditary angioedema
- have kidney or liver problems
- have diabetes
- are pregnant or plan to become pregnant. See **“What is the most important information I should know about sacubitril and valsartan tablets?”**
- are breastfeeding or plan to breastfeed. It is not known if sacubitril and valsartan passes into your breast milk. You should not breastfeed during treatment with sacubitril and valsartan tablets. You and your doctor should decide if you will take sacubitril and valsartan tablets or breastfeed.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Taking sacubitril and valsartan tablets with certain other medicines may affect each other. Taking sacubitril and valsartan tablets with other medicines can cause serious side effects. Especially tell your doctor if you take:

- potassium supplements or a salt substitute
- nonsteroidal anti-inflammatory drugs (NSAIDs)
- lithium
- other medicines for high blood pressure or heart problems, such as an ACE inhibitor, ARB, or aliskiren

Keep a list of your medicines to show your doctor and pharmacist when you get a new medicine.

How should I take sacubitril and valsartan tablets?

- Take sacubitril and valsartan tablets exactly as your doctor tells you to take it.
- Take sacubitril and valsartan tablets 2 times each day. Your doctor may change your dose of sacubitril and valsartan tablets during treatment.
- If you or your child cannot swallow tablets, or if tablets are not available in the prescribed strength, you or your child may take sacubitril and valsartan tablets prepared as a liquid (oral) suspension.
- If you or your child switches between taking sacubitril and valsartan tablets and the liquid suspension prepared from sacubitril and valsartan tablets, your doctor will adjust the dose as needed.
- **If you or your child are prescribed sacubitril and valsartan tablets to be prepared as a liquid suspension:**
 - o Your pharmacist will prepare sacubitril and valsartan tablets for you or your child to take as a liquid suspension.
 - o Shake the bottle of suspension well before measuring the dose of medicine and before taking or giving the dose.
- If you miss a dose, take it as soon as you remember. If it is close to your next dose, do not take the missed dose. Take the next dose at your regular time.
- If you take too many sacubitril and valsartan tablets, call your doctor right away.

What are the possible side effects of sacubitril and valsartan tablets?

Sacubitril and valsartan tablets may cause serious side effects, including:

- See **“What is the most important information I should know about sacubitril and valsartan tablets?”**
- **Serious allergic reactions causing swelling of your face, lips, tongue, and throat (angioedema) that may cause trouble breathing and death.** Get emergency medical help right away if you have symptoms of angioedema or trouble breathing. Do not take sacubitril and valsartan tablets again if you have had angioedema during treatment with sacubitril and valsartan tablets.

People who are Black and take sacubitril and valsartan tablets may have a higher risk of having angioedema than people who are not Black and take sacubitril and valsartan tablets.

People who have had angioedema before taking sacubitril and valsartan tablets may have a higher risk of having angioedema than people who have not had angioedema before taking sacubitril and valsartan tablets. See **“Who should not take sacubitril and valsartan tablets?”**

- **Low blood pressure (hypotension).** Low blood pressure is common during treatment with sacubitril and valsartan tablets. Your risk of low blood pressure is greater if you also take water pills (diuretics). Call your doctor if you become dizzy or lightheaded, or you develop extreme tiredness (fatigue).
- **Kidney problems.** Kidney problems are common during treatment with sacubitril and valsartan tablets and can be serious and can lead to kidney failure. Your doctor will check your kidney function during your treatment with sacubitril and valsartan tablets.
- **Increased amount of potassium in your blood (hyperkalemia).** Increased blood potassium levels are common during treatment with sacubitril and valsartan tablets. Your doctor will check your potassium blood level during your treatment with sacubitril and valsartan tablets.

The most common side effects of sacubitril and valsartan tablets also include cough and dizziness.

Your doctor may need to lower your dose, temporarily stop treatment, or permanently stop treatment if you develop certain side effects or if you have changes in your kidney function or increased blood levels of potassium during treatment with sacubitril and valsartan tablets.

These are not all of the possible side effects of sacubitril and valsartan tablets. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store sacubitril and valsartan tablets?

- Store sacubitril and valsartan tablets at room temperature between 68°F to 77°F (20°C to 25°C).
- Protect sacubitril and valsartan tablets from moisture.
- Store bottles of sacubitril and valsartan tablets prepared as an oral suspension at room temperature less than 77°F (25°C) for up to 15 days. **Do not** refrigerate sacubitril and valsartan tablets prepared as an oral suspension.

Keep sacubitril and valsartan tablets and all medicines out of the reach of children.

General information about the safe and effective use of sacubitril and valsartan tablets.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use sacubitril and valsartan tablets for a condition for which it was not prescribed. Do not g

sacubitril and valsartan tablets to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or doctor for information about sacubitril and valsartan tablets that is written for health professionals.

What are the ingredients in sacubitril and valsartan tablets?

Active ingredients: sacubitril and valsartan

Inactive ingredients: crospovidone, low-substituted hydroxypropylcellulose, magnesium stearate, microcrystalline cellulose, and silicon dioxide. The film-coat inactive ingredients are hypromellose, titanium dioxide, Macrogol 4000, talc, and iron oxide red. 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. The film-coat for the 49 mg of sacubitril and 51 mg of valsartan tablet contains iron oxide yellow.

Prepared sacubitril and valsartan oral suspension also contains Ora-Sweet SF and Ora-Plus.

For more information, call Laurus Generics Inc. at 1-833-3-LAURUS (1-833-352-8787).

This Patient Information has been approved by the U.S. Food and Drug Administration.

Manufactured for:
Laurus Generics Inc.
400 Connell Drive
Suite 5200
Berkeley Heights, NJ 07922

Manufactured by:
Laurus Labs Limited
Anakapalli-531011
India

Revised: 5/2024

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96 mm

22.05 mm

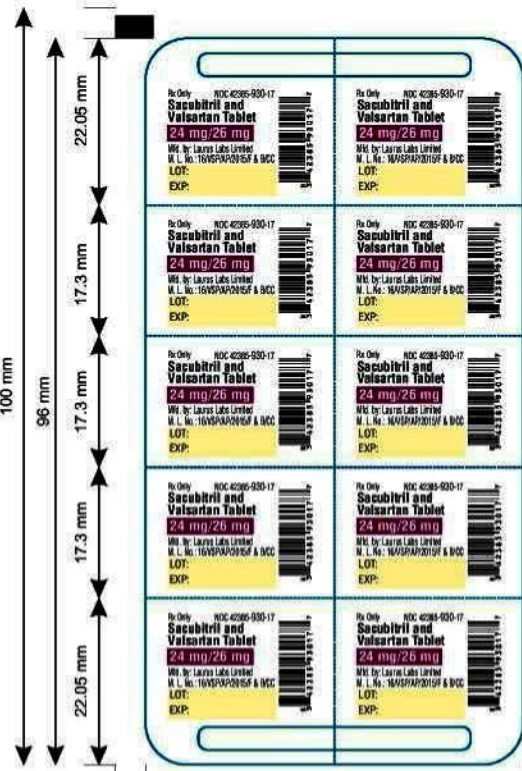
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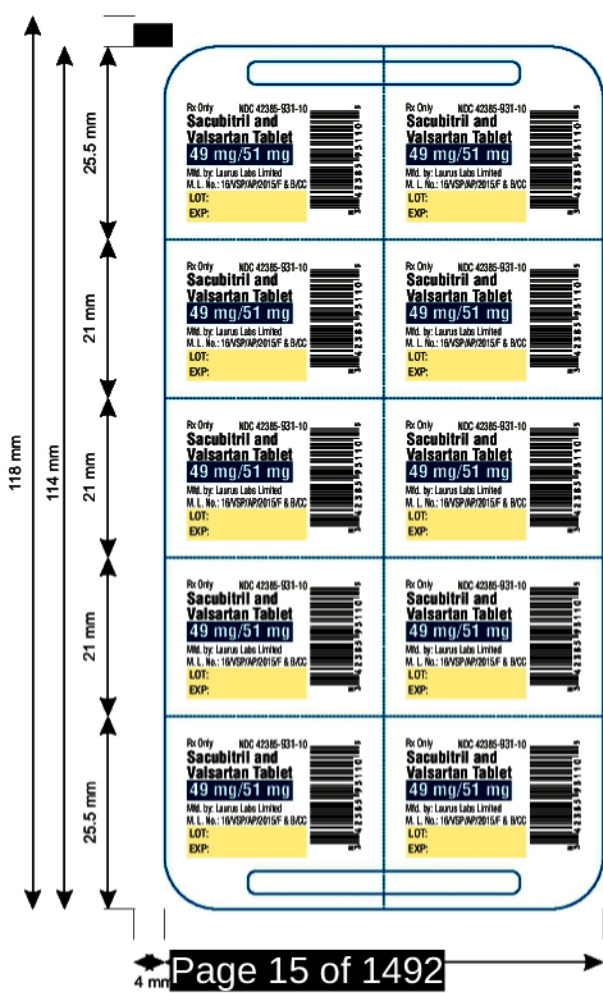
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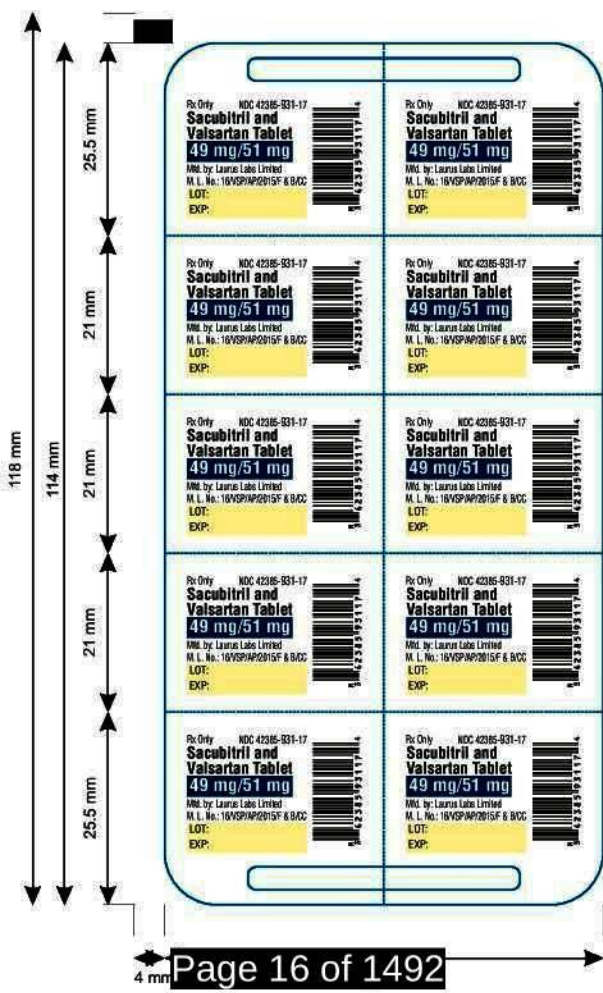
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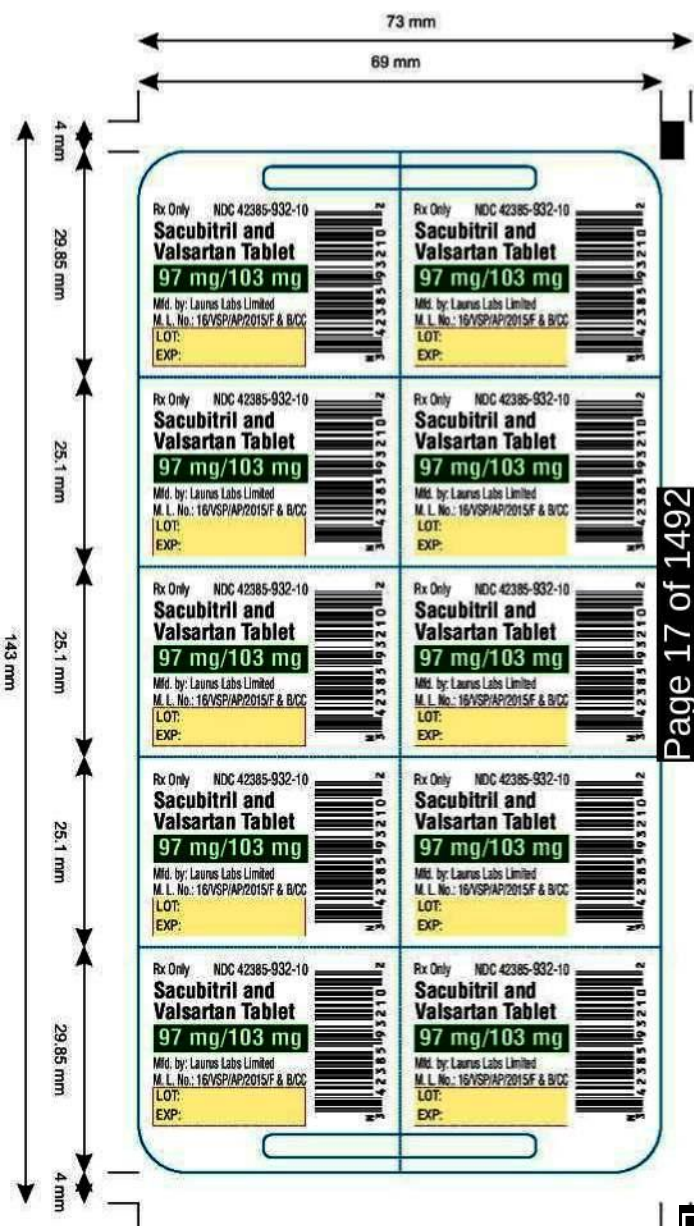




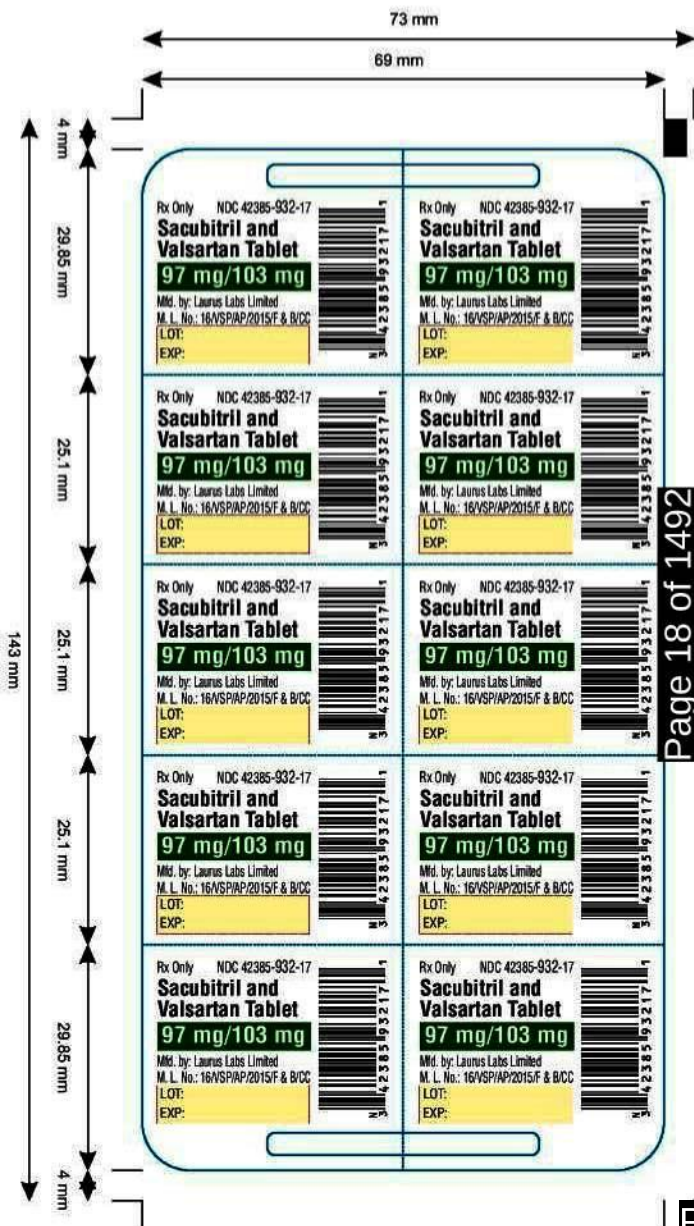
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Rx Only NDC 42385-931-17 Sacubitril and Valsartan Tablet 49 mg/51 mg Mfg. by: Laurus Labs Limited M. L. No.: 18VSPAP2015F & BCC LOT: EXP:	Rx Only NDC 42385-931-17 Sacubitril and Valsartan Tablet 49 mg/51 mg Mfg. by: Laurus Labs Limited M. L. No.: 18VSPAP2015F & BCC LOT: EXP:
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Rx Only NDC 42385-932-17
Sacubitril and Valsartan Tablet
97 mg/103 mg
 Mfd. by: Laurus Labs Limited
 M.L. No.: 16/VSP/AP/2015/F & B/C/C
 LOT:
 EXP:



Rx Only NDC 42385-932-17
Sacubitril and Valsartan Tablet
97 mg/103 mg
 Mfd. by: Laurus Labs Limited
 M.L. No.: 16/VSP/AP/2015/F & B/C/C
 LOT:
 EXP:



Rx Only NDC 42385-932-17
Sacubitril and Valsartan Tablet
97 mg/103 mg
 Mfd. by: Laurus Labs Limited
 M.L. No.: 16/VSP/AP/2015/F & B/C/C
 LOT:
 EXP:



Rx Only NDC 42385-932-17
Sacubitril and Valsartan Tablet
97 mg/103 mg
 Mfd. by: Laurus Labs Limited
 M.L. No.: 16/VSP/AP/2015/F & B/C/C
 LOT:
 EXP:



Rx Only NDC 42385-932-17
Sacubitril and Valsartan Tablet
97 mg/103 mg
 Mfd. by: Laurus Labs Limited
 M.L. No.: 16/VSP/AP/2015/F & B/C/C
 LOT:
 EXP:



Rx Only NDC 42385-932-17
Sacubitril and Valsartan Tablet
97 mg/103 mg
 Mfd. by: Laurus Labs Limited
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Rx Only NDC 42385-932-17
Sacubitril and Valsartan Tablet
97 mg/103 mg
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Rx Only NDC 42385-932-17
Sacubitril and Valsartan Tablet
97 mg/103 mg
 Mfd. by: Laurus Labs Limited
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Rx Only NDC 42385-932-17
Sacubitril and Valsartan Tablet
97 mg/103 mg
 Mfd. by: Laurus Labs Limited
 M.L. No.: 16/VSP/AP/2015/F & B/C/C
 LOT:
 EXP:



Rx Only NDC 42385-932-17
Sacubitril and Valsartan Tablet
97 mg/103 mg
 Mfd. by: Laurus Labs Limited
 M.L. No.: 16/VSP/AP/2015/F & B/C/C
 LOT:
 EXP:



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30 Tablets NDC 42385-8300-30

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

Usual Dosage: See prescribing information.

Store at 20° to 25° C (68° to 77° F); excursions permitted between 15° to 30° C (59° 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.: 16VSRP/2015F & B/CC

105 x 40 mm
CAYK

Manufactured for:
Laurus Generics Inc.
400 Connell Drive
Suite 5200
Berkeley Heights, NJ 07822

Manufactured by:
Laurus Labs Limited
Vishalpatnam-531011
India

ZXXXXXXXX

LOT:
EXP.:



Unreserved Zone
(48 x 15 mm)

Sacubitril and Valsartan Tablets

24 mg/26 mg

Rx Only



Page 19 of 1492

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

Usual Dosage: See prescribing information.

Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° 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.: 16/VSP/AP/2015/F & B/CC

105 x 40 mm
OMK

60 Tablets NDC 42935-930-60

Sacubitril and Valsartan Tablets

24 mg/26 mg

Rx Only



Manufactured for:
Laurus Biomedica Inc.
403 Connel Drive
Suite 5200
Berkeley Heights, NJ 07922
Manufactured by:
Laurus Labs Limited
Vasohapatnam-531011
India
Z00000



Unretrieved Zone
(45 x 15 mm)

LOT:
EXP:

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

Usual Dosage: See prescribing information.

Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° 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.: 16/MSP/AP/2015/F & B/CC

135 x 48 mm
CHK

180 Tablets

NDC 42385-930-18
Manufactured for:
Laurus Generics Inc.
407 Cornwell Drive
Suite 5200
Berkeley Heights, NJ 07802
Manufactured by:
Laurus Labs Limited
Vishakhapatnam-530011
INDIA
Zxxxxx

Sacubitril and Valsartan Tablets

24 mg/26 mg

Rx Only



Unrestricted Zone
(45 x 15 mm)

LOT:

EXP:

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30 Tablets NDC 42385-931-30

Each film-coated tablet contains:
49 mg sacubitril and 51 mg
valsartan.

Usual Dosage: See prescribing
information.

Store at 20° to 25°C (68° to 77°F);
excursions permitted between
15° to 30°C (59° 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.: 16/VSP/AP/2015/F&B/CC

106 x 40 mm
CMVK

Manufactured by:
Laurus Generics Inc.
401 Central Drive
Suite 5200
Berkeley Heights, NJ 07922

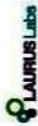
Manufactured by:
Laurus Labs Limited
Vishakhapatnam-531011
India
200000

LOT:

EXP.:



Unreserved Zone
(45 x 10 mm)



Rx Only

Sacubitril and Valsartan Tablets

49 mg/51 mg

Page 22 of 1492

Each film-coated tablet contains 49 mg sacubitril and 51 mg valsartan.

Usual Dosage: See prescribing information.

Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° 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.: 16/VSP/AP/2015/F&B/CC

105 x 40 mm
CMVX

60 Tablets NDC 42385-331-60

Sacubitril and Valsartan Tablets

49 mg/51 mg

Rx Only



Manufactured for:
Laurus Generics Inc.
400 Central Drive
Suite 5200
Berkeley Heights, NJ 07922
Manufactured by:
Laurus Labs Limited
Visakhapatnam-531011
India
200000

LOT:

EXP:



Manufactured Zone
(48 ± 10 mm)

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Each film-coated tablet contains 49 mg sacubitril and 51 mg valsartan.

Usual Dosage: See prescribing information.

Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° 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.: 16/SP/AP/2015/F & B/C/C

180 Tablets NDC 42385-931-18

Sacubitril and Valsartan Tablets

49 mg/51 mg

Rx Only



Manufactured for:
Laurus Generics Inc.
400 Cornell Drive
Suite 5200
Berkeley Heights, NJ 07922
Manufactured by:
Laurus Labs Limited
Vishnupatnam-531011
India
200000X

LOT:
EXP:

Unpackaged Zone
(45 x 18 mm)



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120 x 40 mm
CMK

Each film-coated tablet contains 97 mg sacubitril and 103 mg valsartan.

Usual Dosage: See prescribing information.

Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° 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.: 16VSP/AP/2015/F & B/C

30 Tablets

NDC 42365-532-30

Sacubitril and Valsartan Tablets

97 mg/103 mg

Rx Only



Manufactured for:
Laurus Generics Inc.
400 Cornwell Drive
Suite E200
Berkeley Heights, NJ 07922
Manufactured by:
Laurus Labs Limited
Visakhapatnam-531011
India
Zxxxxx

LOT:
EXP:



Unwrap/Unsealed Zone
(45 x 15 mm)

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106 x 40 mm
CMVX

Each film-coated tablet contains 97 mg sacubitril and 103 mg valsartan.

Usual Dosage: See prescribing information.

Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° 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.: 16/NSP/AP/2015.F & B/CC

105 x 40 mm
DMK

60 Tablets NDC 43285-932-60

Sacubitril and Valsartan Tablets

97 mg/103 mg

Rx Only
LAURUS Labs

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Manufactured by:
Laurus Biogenics Inc.
400 Cornell Drive
Berkeley Heights, NJ 07822
Manufactured by:
Laurus Labs Limited
Vishkapatnam-531011
India
Zxxxxxx

LOT:
EXP:



Unassembled Zone
(45 ± 15 mm)

Each film-coated tablet contains 97 mg sacubitril and 103 mg valsartan.

Usual Dosage: See prescribing information.

Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° 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.: 16/SP/AP/2015/F & B/C

NDC 42385-932-18

Manufactured for:
Laurus Generics Inc.
400 Cornell Drive
Suite 5200
Berkeley Heights, NJ 07922
Manufactured by:
Laurus Labs Limited
Visakhapatnam-531011
India

2XXXXX

LOT:
EXP:



Unpackaged Zone
(46 x 15 mm)

Rx Only



Page 27 of 1492

120 x 40 mm
CMX

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B.No.:
Mfg.:
Exp:

Batch coding details
will be printed online



NDC 42385-930-68

Sacubitril and Valsartan Tablets

24 mg/26 mg

For Institutional Use Only.

100 (10 x 10) Unit-Dose Tablets

Rx Only

Space for Pharma code

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

Usual Dosage: See prescribing information.

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

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

2000XXX



NDC 42385-930-68

Sacubitril and Valsartan Tablets

24 mg/26 mg

For Institutional Use Only.

100 (10 x 10) Unit-Dose Tablets

Rx Only

Space for Pharma code

For Institutional Use Only.

24 mg/26 mg

Sacubitril and Valsartan
Tablets

Manufactured for:
Laurus Generics Inc.
400 Connell Drive
Suite 5200
Berkeley Heights, NJ 07922

Manufactured by:
Laurus Labs Limited
Visakhapatnam-531011
India



M. L. No.: 16/VSP/AP/2015/F & B/CC

B.No.:
Mfg.:
Exp:

Batch coding details
will be printed online



NDC 42385-930-72

Sacubitril and Valsartan Tablets

24 mg/26 mg

For Institutional Use Only.

100 (10 x 10) Unit-Dose Tablets

Rx Only

Space for Pharma code

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

Usual Dosage: See prescribing information.

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

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

2000XXX



NDC 42385-930-72

Sacubitril and Valsartan Tablets

24 mg/26 mg

For Institutional Use Only.

100 (10 x 10) Unit-Dose Tablets

Rx Only

Space for Pharma code

For Institutional Use Only.

24 mg/26 mg

**Sacubitril and Valsartan
Tablets**

Manufactured for:
Laurus Generics Inc.
400 Connell Drive
Suite 5200
Berkeley Heights, NJ 07922

Manufactured by:
Laurus Labs Limited
Visakhapatnam-531011
India



N 3 42385 193072 16

M. L. No.: 16/VSP/AP/2015/F & B/CC

B.No.:
Mfg.:
Exp:

Space for Pharma code

NDC 42385-931-68



Sacubitril and Valsartan Tablets

49 mg/51 mg

For Institutional Use Only.

100 (10 x 10) Unit-Dose Tablets **Rx Only**

Each film-coated tablet contains
49 mg sacubitril and 51 mg valsartan.

Usual Dosage: See prescribing information.

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

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

2000XXX



NDC 42385-931-68

Sacubitril and Valsartan Tablets

49 mg/51 mg

For Institutional Use Only.

100 (10 x 10) Unit-Dose Tablets **Rx Only**

Manufactured for:
Laurus Generics Inc.
400 Connell Drive
Suite 5200
Berkeley Heights, N.J. 07922

Sacubitril and Valsartan Tablets

49 mg/51 mg

For Institutional Use Only.

Space for Pharma code

B.No.:
Mfg.:
Exp:

Batch coding details
will be printed online

Space for Pharma code

NDC 42385-931-72



Sacubitril and Valsartan Tablets

49 mg/51 mg

For Institutional Use Only.

Rx Only

100 (10 x 10) Unit-Dose Tablets

Each film-coated tablet contains
49 mg sacubitril and 51 mg valsartan.

Usual Dosage: See prescribing information.

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

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

2000XXX

NDC 42385-931-72



Sacubitril and Valsartan Tablets

49 mg/51 mg

For Institutional Use Only.

Rx Only

100 (10 x 10) Unit-Dose Tablets

Manufactured for:
Laurus Generics Inc.
400 Connell Drive
Suite 5200
Berkeley Heights, NJ 07922

Sacubitril and Valsartan Tablets

49 mg/51 mg

For Institutional Use Only.

Space for Pharma code

B.No.:
Mfg.:
Exp:



NDC 42385-932-68

Sacubitril and Valsartan Tablets

97 mg/103 mg

For Institutional Use Only.

100 (10 x 10) Unit-Dose Tablets

Rx Only

Each film-coated tablet contains
97 mg sacubitril and 103 mg valsartan.

Usual Dosage: See prescribing information.

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

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

2000XXX



NDC 42385-932-68

Sacubitril and Valsartan Tablets

97 mg/103 mg

For Institutional Use Only.

Sacubitril and Valsartan Tablets

97 mg/103 mg

For Institutional Use Only.

Space for Pharma code

B.No.:
Mfg.:
Exp:



NDC 42385-932-72

Sacubitril and Valsartan Tablets

97 mg/103 mg

For Institutional Use Only.

100 (10 x 10) Unit-Dose Tablets

Rx Only

Each film-coated tablet contains
97 mg sacubitril and 103 mg valsartan.

Usual Dosage: See prescribing information.

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

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

2000XXX



NDC 42385-932-72

Sacubitril and Valsartan Tablets

97 mg/103 mg

For Institutional Use Only.

Sacubitril and Valsar Tablets

97 mg/103 mg

For Institutional Use On

Space for Pharma code

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 213676

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	10/01/2019
ANDA Number(s)	213676
Review Number	1
Applicant Name	Laurus Labs 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	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 [†]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 October 1, 2019, based on your submission received July 8, 2019:

1. CONTAINERS 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg in bottles of 30s, 60s, and 180s.
 - a. Relocate the net quantity statement to the bottom portion of label or very top (on same line as NDC statement) further away from the declaration of strength statement to prevent medication errors.
 - b. Insert a hyphen in "film-coated" and revise the "Each film-coated tablet..." statements so that the amount of active ingredient is consistent with the Description section in the insert. (b)(4)

2. UNIT DOSE BLISTERS and CARTONS, 100s (10 x10 unit dose blisters)

- a. Revise "Each film-coated tablet contains..." statements so that the amount of active is consistent with the insert, description section. (b)(4)

b.

(b)(4)

3. PRESCRIBING INFORMATION

- a. Revise your labeling to be in accordance with the labeling for the reference listed drug (RLD), Entresto (sacubitril and valsartan) tablets, NDA 207620/S-013, approved 10/1/2019. Labeling is posted at Drugs@FDA website.
- b. Please address any updates to the OB listing.
- c. In addition to the above changes, please note the following minor editorial change request: HIGHLIGHTS, title line, replace "TABLETS" with lower case letters "tablets". See the RLD labeling for guidance.

d.

(b)(4)

4. PATIENT LEAFLET- See comments under prescribing information.

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.

I.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.

I.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.

4/19/2019

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/SE-013

Supplement Approval Date: 10/1/2019

Proprietary Name: Entresto® (sacubitril/valsartan), Tablets.

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.

S-008, approved 11/22/2017

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

This supplemental new drug application provides for revisions to the approved labeling as follows (additions are shown as underlined text and deletions are shown as ~~strikethrough~~ text):

1. Under **WARNINGS AND PRECAUTIONS/Angioedema**, the following text was added to the last paragraph:

Patients with a prior history of angioedema may be at increased risk of angioedema with ENTRESTO [see Adverse Reactions (6.1)]. ENTRESTO ~~should~~ must not be used in patients with a known history of angioedema related to previous ACE inhibitor or ARB therapy [see Contraindications (4)]. ENTRESTO should not be used in patients with hereditary angioedema.

2. Under **ADVERSE REACTIONS**, the following section was added:

6.2 Postmarketing Experience

The following additional adverse reactions have been reported in postmarketing experience. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypersensitivity, including rash, pruritus and anaphylactic reaction

The following revision was made to the Entresto Patient Package Inset:

3. Under **What should I tell my doctor before taking ENTRESTO?** the following bullet was added:
 - have a history of hereditary angioedema
4. The **CONTENTS** section was updated to reflect the addition of the new section (6.2).
5. The revision date and version numbers were updated.

There are no other changes from the last approved package insert.

OTHER IMPORTANT INFORMATION:

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

(b)(4)

Drug product section 3.2.P.7 also updated for addition of 60 cc (b)(4) bottles, addition of 28 count physician sample pack (b)(4) and 49/51 mg (b)(4) of physician sample pack (b)(4)

Supplements 14 to 15 (CMC supplements): PENDING 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.

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

OTHER (Describe):

2.2.2 MODEL CONTAINER LABELS

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

0078-0659-67
Entresto®
 (sacubitril/valsartan)
 tablets
24mg/26mg
 Rx only
 180 Tablets

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 121253 US

**Physician Sample
 Not for Sale**
Entresto®
 (sacubitril/valsartan)
 tablets
24mg/26mg
 Rx only 28 Tablets

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 US

0078-0659-20
Entresto®
 (sacubitril/valsartan)
 tablets
24mg/26mg
 Rx only
 60 Tablets

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

0078-0777-67
Entresto®
 (sacubitril/valsartan)
 tablets
49mg/51mg
 Rx only
 180 Tablets

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

Physician Sample
Not for Sale



EXPI. LOT:



Entresto®
(sacubitril/valsartan)
tablets

49 mg/51 mg

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 US

NDC 0078-0777-20



EXPI. LOT:

GTIN: 00300780777209



Entresto®
(sacubitril/valsartan)
tablets

49 mg/51 mg

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

NDC 0078-0696-67



EXPI. LOT:

GTIN: 00300780696678



Entresto®
(sacubitril/valsartan)
tablets

97 mg/103 mg

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

NDC 0078-0696-20



EXPI. LOT:

GTIN: 00300780696203



Entresto®
(sacubitril/valsartan)
tablets

97 mg/103 mg

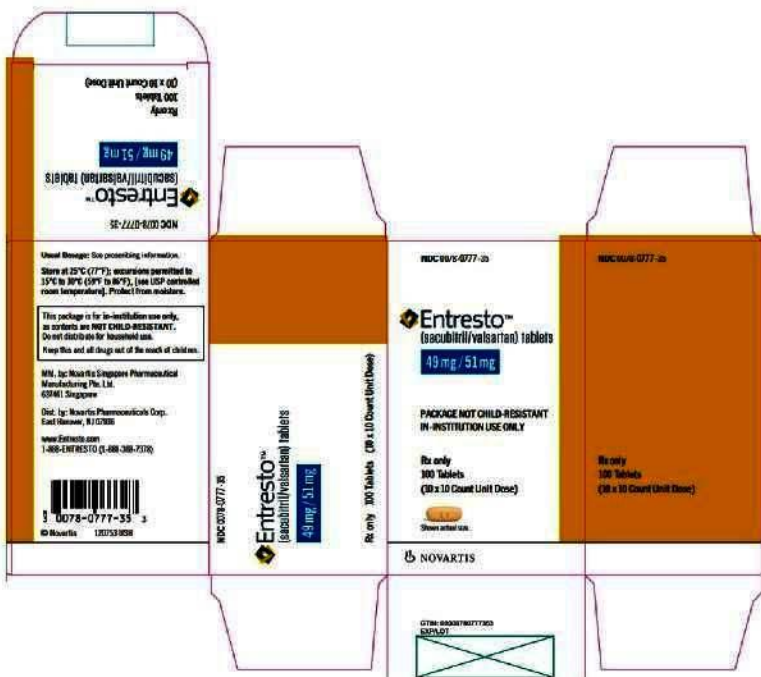
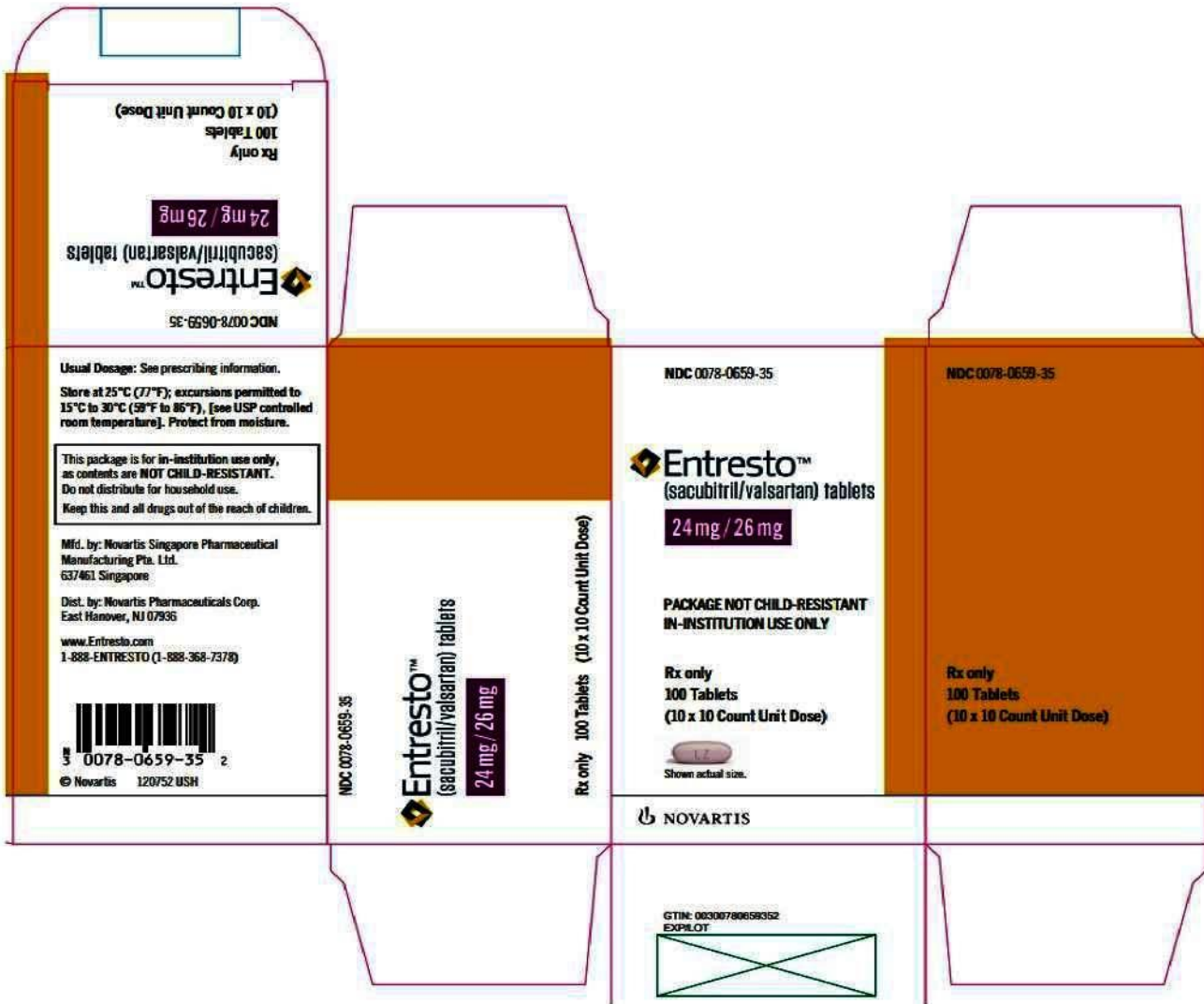
Rx only 60 Tablets

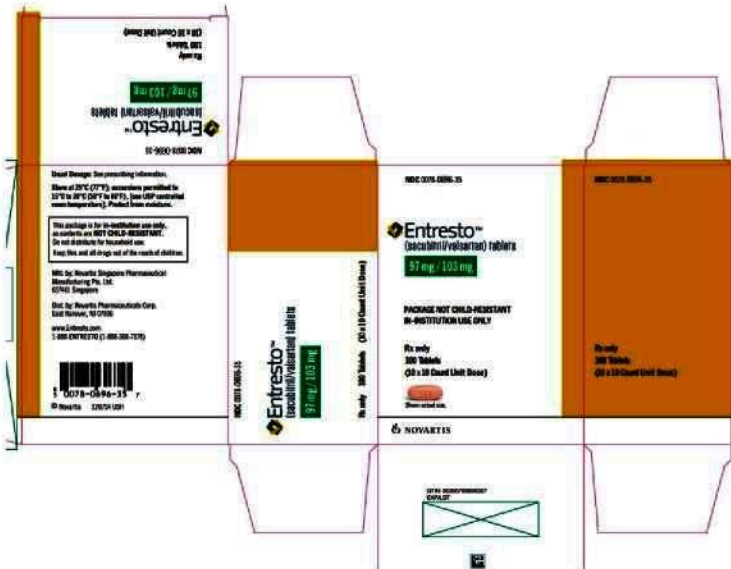


NOVARTIS

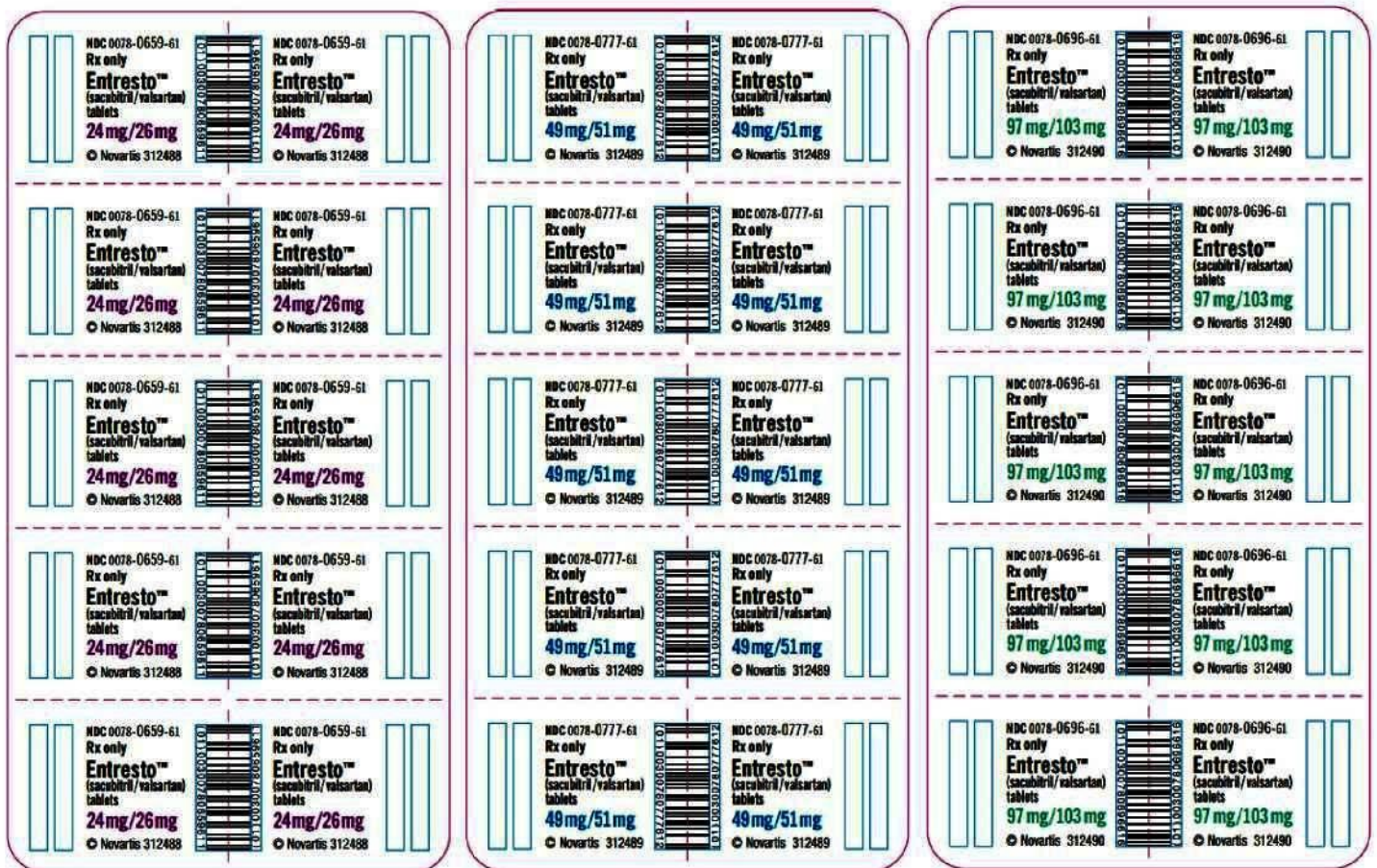
Usual Dosage: See prescribing information.
Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). [See USP controlled room temperature].
Protect from moisture.
Keep this and all drugs out of the reach of children.
Mfd. by: Novartis Singapore Pharmaceutical Manufacturing Pte. Ltd., 637461 Singapore
Dist. by: Novartis Pharmaceuticals Corp. East Hanover, NJ 07936
www.Entresto.com
1-888-ENTRESTO (1-888-368-7378)
© Novartis 121256 US

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





Model container/carton/blister labels (Source: DARRTS; ANRPT-1 submitted 8/30/2016)



2.3 UNITED STATES PHARMACOPEIA (USP)

The USP was searched on 10/2/2019.

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 10/2/2019.

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 PED 05/27/2024			IV	7/8/2019	None
8101659	2023-01-14 Ped 7/14/2023			IV	7/8/2019	None
8404744	2023-01-14 PED 7/14/2023			IV	7/8/2019	None
8796331	2023-01-14 PED 7/14/2023	U-1723	TREATMENT OF HEART FAILURE	IV	7/8/2019	None
8877938	2027-05-27 PED 11/27/2027			IV	7/8/2019	None
9388134	2026-11-08 PED 05/08/2027	U-1723	TREATMENT OF HEART FAILURE	IV	7/8/2019	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	2020-07-07	NEW CHEMICAL ENTITY	does not intend to market its proposed prior to the expiration of the NCE 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

Laurus Labs Limited 2nd Floor, Serene Chambers, Road No. 7 Banjara Hills, Hyderabad - 500034, Telangana, India (IND).	Manufactured for: Laurus Generics Inc. 400 Connell Drive Suite 5200 Berkeley Heights, NJ 07922 Manufactured by: (b)(4)	Manufactured for: Laurus Generics Inc. 400 Connell Drive Suite 5200 Berkeley Heights, NJ 07922 Manufactured by: (b)(4)

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:

- On 10/1/2019 an efficacy supplement for pediatric use and indication was approved for the NDA. ANDA will be requested to revise accordingly. In addition, we anticipate H/W pediatric exclusivity will be posted in the OB.
- Minor editorial change needed under HIGHLIGHTS, title line, dosage form “tablets” rather than TABLETS. This type of change editorial and based on labeling tools guidance. Because the insert has to be revised based on new updates, we will be issued the following comment: PROFESSIONAL LABELING - HIGHLIGHTS, title line, replace “TABLETS” with lower case letters “tablets”. See the RLD labeling for guidance.

- **(b)(4)**

3.1.1.1 RX: DESCRIPTION

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

Model Labeling	ENTRESTO contains a complex comprised of anionic forms of sacubitril and valsartan, sodium cations, and water molecules in the molar ratio of 1:1:3:2.5, respectively. Following oral administration, the complex dissociates into sacubitril (which is further metabolized to LBQ657) and valsartan. The complex is chemically described as Octadecasodiumhexakis(4-(((1S,3R)-1-((1,1'-biphenyl)-4-ylmethyl)-4-ethoxy-3-methyl-4-oxobutyl)amino)-4-oxobutanoate)hexakis(N-pentanoyl-N-((2'-(1H-tetrazol-1-yl-5-yl)[1,1'-biphenyl]-4-yl)methyl)-L-valinate)—water (1/15). Its empirical formula (hemipentahydrate) is C₄₈H₅₅N₆O₈Na₃ 2.5H₂O. Its molecular mass is 957.99 and its schematic structural 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 filmcoat inactive ingredients are hypromellose, titanium dioxide (E 171), Macrogol 4000, talc, and iron oxide red (E 172). The filmcoat 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	anionic forms of sacubitril and valsartan, and sodium cations in the molar ratio of 1:1:3, respectively. Following oral administration, the complex dissociates into sacubitril (which is further metabolized to LBQ657) and valsartan. The complex is chemically described as Tri sodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate]. Its molecular formula is C₄₈H₅₅N₆O₈•3Na. Its molecular mass is 912.95 and its schematic structural formula is: (b) (4)

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:

- (b) (4)**

(b)(4)

3.2.P.1.2 Composition of the Drug Product

The Qualitative and Quantitative Composition of Sacubitril and Valsartan Tablets 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg along with the function of each component are listed below:

Ingredients	Compendial Reference	Pharmaceutical Function	24mg/ 26mg	49mg/ 51mg	97mg/ 103mg	%w/w
			(mg/ Tablet)			
(b)(4)						
Sacubitril-Valsartan (b)(4)	In-House	Active Ingredient	(b)(4)			
Low-substituted hydroxypropylcellulose (b)(4)	USP-NF					
Microcrystalline Cellulose (b)(4)	USP-NF					
Crospovidone (b)(4)	USP-NF	(b)(4)				
Silicon dioxide (b)(4)	USP-NF					
Magnesium Stearate (b)(4)	USP-NF					
(b)(4)						
(b)(4)		(b)(4)	(b)(4)			
(b)(4)						
(b)(4)		(b)(4)	(b)(4)			
Weight of Coated Tablet			103.000	206.000	412.000	100.000

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)

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	Bottle of 180	Blister Packages of 100
	24 mg/26 mg	Violet white	LZ	0659-20	0659-67	0659-35
	49 mg/51 mg	Pale yellow	L1	0777-20	0777-67	0777-35
97 mg/103 mg	Light pink	L11	0696-20	0696-67	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.						

Table 7: Comparison of Model Labeling to ANDA Labeling

ANDA Labeling	16 HOW SUPPLIED/STORAGE AND HANDLING Sacubitril and valsartan tablets are available as described below: Sacubitril and valsartan tablets 24/26 mg, (sacubitril 24 mg and valsartan 26 mg) are violet white color, oval shaped, biconvex film-coated tablets debossed with "S5" on one side and plain on the other side. Bottles of 30 NDC 42385-930-30 Bottles of 60 NDC 42385-930-60 Bottles of 180 NDC 42385-930-18 Carton with 100 (10 x 10) Unit-Dose Tablets containing cold form with desiccant blisters NDC 42385-930-68 Carton with 100 (10 x 10) Unit-Dose Tablets containing PVC/ACLAR blisters NDC 42385-930-72 Sacubitril and valsartan tablets 49/51 mg, (sacubitril 49 mg and valsartan 51 mg) are pale yellow color, oval shaped, biconvex film-coated tablets debossed with "S1" on one side and plain on the other side. Bottles of 30 NDC 42385-931-30 Bottles of 60 NDC 42385-931-60 Bottles of 180 NDC 42385-931-18 Carton with 100 (10 x 10) Unit-Dose Tablets containing cold form with desiccant blisters NDC 42385-931-68 Carton with 100 (10 x 10) Unit-Dose Tablets containing PVC/ACLAR blisters NDC 42385-931-72 Sacubitril and valsartan tablets 97/103 mg, (sacubitril 97 mg and valsartan 103 mg) are light pink color, oval shaped, biconvex film-coated tablets debossed with "S2" on one side and plain on the other side. Bottles of 30 NDC 42385-932-30 Bottles of 60 NDC 42385-932-60 Bottles of 180 NDC 42385-932-18 Carton with 100 (10 x 10) Unit-Dose Tablets containing cold form with desiccant blisters NDC 42385-932-68 Carton with 100 (10 x 10) Unit-Dose Tablets containing PVC/ACLAR blisters NDC 42385-932-72 Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature]. Protect from moisture.

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? **NO**
 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: The RLD proposes 60s, 180s, and UD (institutional) while the ANDA is proposing 30s (b)(4) 60s (b)(4) and 180s (b)(4) and UD. The 30 count appears reasonable for this drug product.

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? **CLICK HERE**
Is the Medication Guide same as the model labeling, except for allowable differences? **CLICK HERE**
Has the Applicant committed to provide a sufficient number of medication guides? **CLICK HERE**
Is the phonetic spelling of the proprietary or established name present? **CLICK HERE**
Is FDA 1-800-FDA-1088 phone number included? **CLICK HERE**

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? **YES**

Reviewer Comments: Updates to the RLD PI occurred on 10/1/2019. Applicant will be requested to revise their labeling. (b)(4)

(b)(4)

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: **NO**
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\(d\)](#): **NA**
[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? **YES**
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:

This ANDA is proposes 30s, 60s, 180s, UD 100s While the RLD markets 60s, 180s and UD 100s. The package size of 30s appears to be a reasonable difference in package size from the RLD. There are no safety concerns for 30s (b)(4)

- (b)(4)
- (b)(4) See comment to applicant above. The container labels are inadequate.
- The net quantity statement is in-close proximity to the declaration of strength. relocate to the bottom part of the labeling or top part near NDC numbers.

Bottles labels and UD carton labeling are inadequate.

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? **YES**
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)? **YES**
Do proprietary name, established name, strength, bar code, and manufacturer/distributor/packer appear accurately on each blister cell? **YES**

Reviewer Comments: None.

3.1.6 RX: CARTON (OUTER OR SECONDARY PACKAGING) LABELING

Was carton labeling submitted? **YES**
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? **YES** 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 Comment: (b)(4)

(b)(4)

(b)(4)

We will ask for a revision.

UD carton labeling are in-adequate.

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 201.23\(c\)\(2\)](#): [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.
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 [\(b\)\(4\)](#) 100s [\(b\)\(4\)](#)) 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: 30s, 60s, 180s (b)(4) Unit dose blisters 100 (10x10s) Module 3.2.P.1

The primary packaging material components were required to meet the established specifications.

(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 Product in 3.2.P.1, and Commercial Batch Record in 3.2.P.3.3)
24 mg/26 mg	S5; 9mm; no score	See below
49 mg/51 mg	S1; 12 mm; no score	
97 mg/103 mg	S2; 15 mm; no score	

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:

3.2.P.1.1 Description of the Drug Product

Product Name		Sacubitril and Valsartan Tablets
Strengths		24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg
Route of Administration		Oral
Description	24 mg/26 mg	Violet white color, oval shaped, biconvex film-coated tablets debossed with "S5" on one side and plain on the other side.
	49 mg/51 mg	Pale yellow color, oval shaped, biconvex film-coated tablets debossed with "S1" on one side and plain on the other side.
	97 mg/103 mg	Light pink color, oval shaped, biconvex film-coated tablets debossed with "S2" on one side and plain on the other side.

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: To OPQ- This just a FYI that the description section in the labeling is noted as having differences from the RLD. Please provide the applicant guidance if the description difference should change to reflect the RLD or if the description is allowable difference. The labeling reviewer defers to the quality assessor for changes in the description and did not make any comment to the applicant.

(b)(4)

(b)(4)

DLR has requested a change to the container labels to be consistent with the applicant's insert labeling.

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 in 30s (b)(4) 60s (b)(4) and 180s (b)(4) count bottles)	July 8, 2019	Revise
Blister	NA	10s cold form and 10s pvc/aclar	July 8, 2019	Satisfactory
Carton	NA	100s	July 8, 2019	Revise
(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	Final	06/2019	July 8, 2019	Revise
Medication Guide	NA			
Patient Information	Final	Revised: 6/2019	July 8, 2019	Revise
SPL Data Elements	Final	June 2019	July 8, 2019	Satisfactory



Angela
Payne

Digitally signed by Angela Payne
Date: 10/24/2019 12:00:41PM
GUID: 508da70600028ab611d2ba935d5074a6



Betty
Turner

Digitally signed by Betty Turner
Date: 10/24/2019 12:33:28PM
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	3/30/2020
ANDA Number(s)	213676
Review Number	2
Applicant Name	Laurus Labs 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	11/07/2019
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 [†] 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 submission (s) received November 07, 2019.

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

(b)(4)

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:

Labeling Deficiencies determined on October 1, 2019, based on your submission received July 8, 2019:

1. CONTAINERS 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg in bottles of 30s, 60s, and 180s.

a. Relocate the net quantity statement to the bottom portion of label or very top (on same line as NDC statement) further away from the declaration of strength statement to prevent medication errors.

b. Insert a hyphen in “film-coated” and revise the “Each film-coated tablet...” statements so that the amount of active ingredient is consistent with the Description section in the insert. (b)(4)

(b)(4)

2. UNIT DOSE BLISTERS and CARTONS, 100s (10 x10 unit dose blisters)

a. Revise “Each film-coated tablet contains...” statements so that the amount of active is consistent with the insert, description section. (b)(4)

(b)(4)

3. PRESCRIBING INFORMATION

a. Revise your labeling to be in accordance with the labeling for the reference listed drug (RLD), Entresto (sacubitril and valsartan) tablets, NDA 207620/S-013, approved 10/1/2019. Labeling is posted at Drugs@FDA website.

b. Please address any updates to the OB listing.

c. In addition to the above changes, please note the following minor editorial change request: HIGHLIGHTS, title line, replace “TABLETS” with lower case letters “tablets”. See the RLD labeling for guidance.

(b)(4)

4. PATIENT LEAFLET- See comments under prescribing information.

Applicants 11/7/2019 response to cycle 1 deficiencies (2b): Unit dose cartons comment-

(b)(4)

3/30/2020 Reviewer's assessment: Applicant responded to the deficiencies from cycle 1. The container, blisters, cartons, insert and patient leaflet are adequate.

- While the applicant stated their product carton blister labels matches the RLD, it is noted comment 2b above (highlight) for the carton will be addressed as a post approval change addressing the blue highlighted deficiency comment above.

-

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: Deficiencies from cycle 1 were addressed in cycle 2. Container labels, unit dose blisters and cartons labels are adequate.

(b)(4)

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:

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. Check PAL#03302020

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 on the Susceptibility Test Interpretive Criteria web page? NO

3.2 MODEL LABELING

**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/SE-013

Supplement Approval Date: 10/1/2019

Proprietary Name: Entresto® (sacubitril/valsartan), Tablets.

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.

S-008, approved 11/22/2017

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

This supplemental new drug application provides for revisions to the approved labeling as follows (additions are shown as underlined text and deletions are shown as ~~strikethrough~~ text):

1. Under **WARNINGS AND PRECAUTIONS/Angioedema**, the following text was added to the last paragraph:

Patients with a prior history of angioedema may be at increased risk of angioedema with ENTRESTO [see Adverse Reactions (6.1)]. ENTRESTO ~~should~~ must not be used in patients with a known history of angioedema related to previous ACE inhibitor or ARB therapy [see Contraindications (4)]. ENTRESTO should not be used in patients with hereditary angioedema.

2. Under **ADVERSE REACTIONS**, the following section was added:

6.2 Postmarketing Experience

The following additional adverse reactions have been reported in postmarketing experience. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypersensitivity, including rash, pruritus and anaphylactic reaction

The following revision was made to the Entresto Patient Package Inset:

3. Under **What should I tell my doctor before taking ENTRESTO?** the following bullet was added:
 - have a history of hereditary angioedema
4. The **CONTENTS** section was updated to reflect the addition of the new section (6.2).
5. The revision date and version numbers were updated.

There are no other changes from the last approved package insert.

OTHER IMPORTANT INFORMATION:

Supplement 16 (CBE-30 CMC supplement): PENDING; (b)(4)

(b) (4)

Supplements 14 to 15 (CMC supplements): PENDING 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.

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

(b)(4)

OTHER (Describe):

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? **YES**

Reviewer Comments:

The proposed template models the RLD S-013. This NPP is being retained in the labeling. (b)(4)

(b)(4) The insert and medication guide are adequate.

3.3 MODEL CONTAINER LABELS

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





 NDC 0078-0659-20
Entresto®
 (sacubitril/valsartan)
 tablets
24 mg/26 mg
 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



 NDC 0078-0777-67
Entresto®
 (sacubitril/valsartan)
 tablets
49 mg/51 mg
 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



 Physician Sample
 Not for Sale
Entresto®
 (sacubitril/valsartan)
 tablets
49 mg/51 mg
 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 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 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

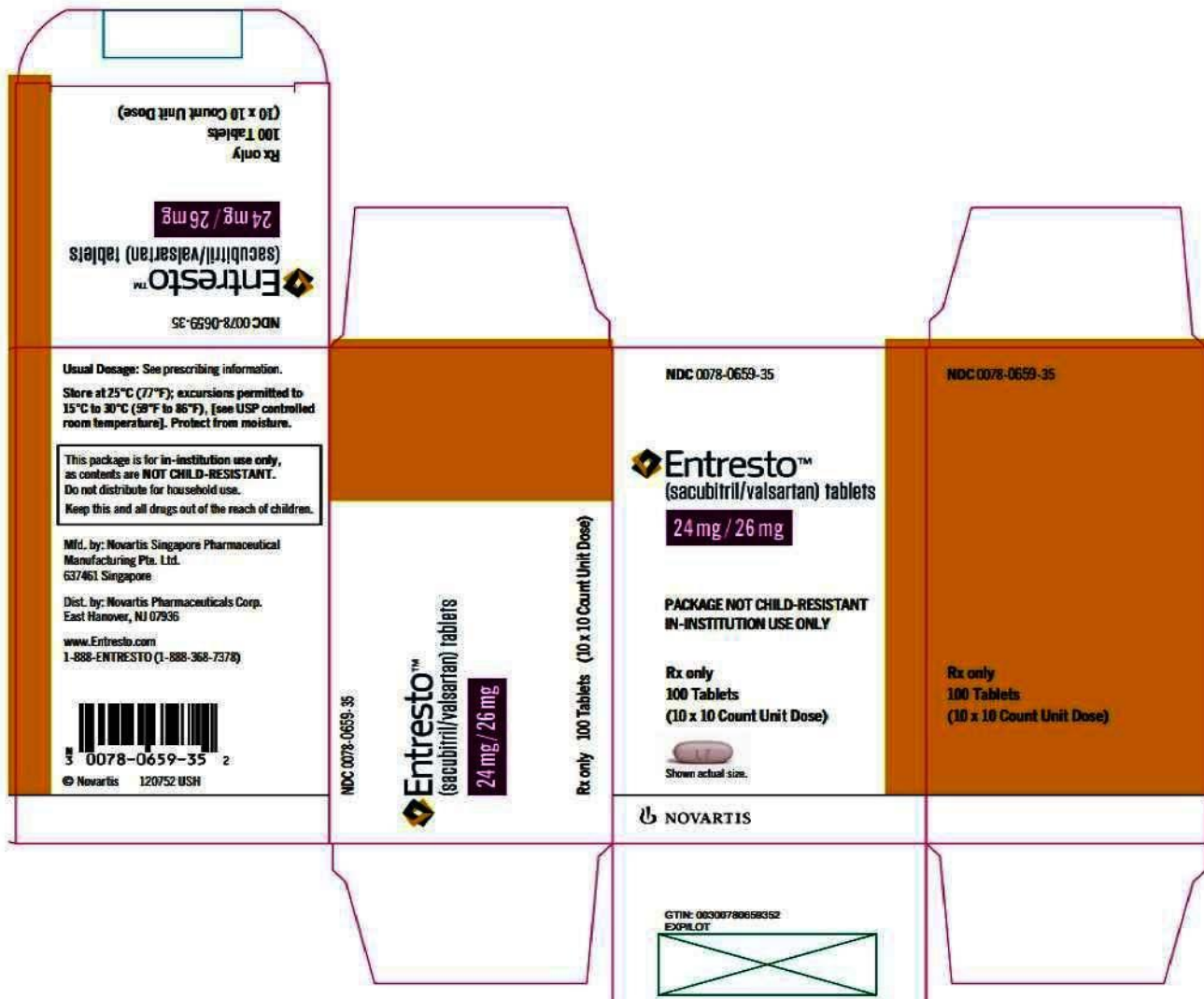


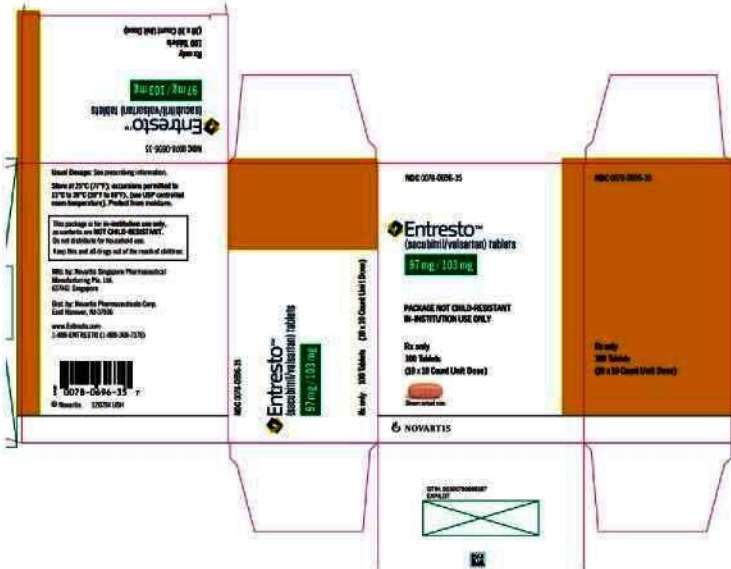
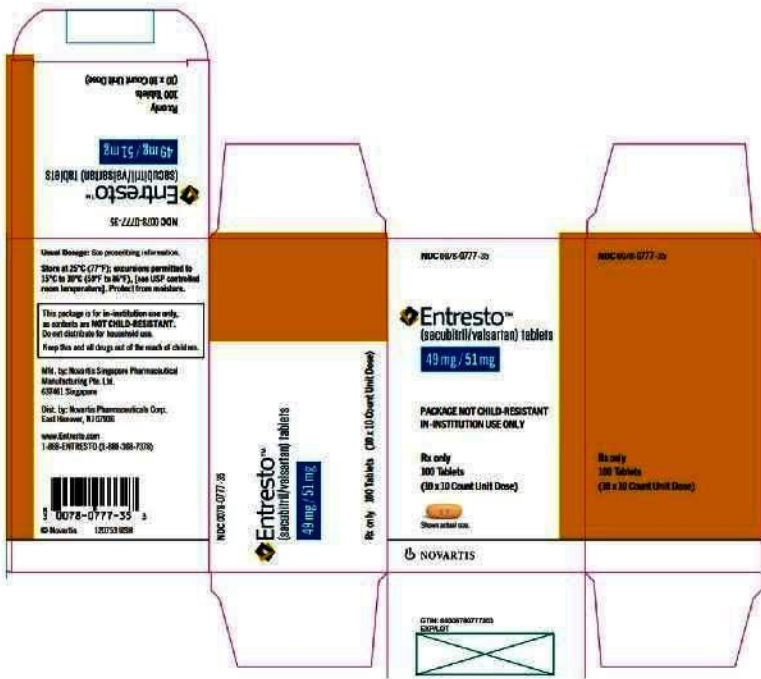
 NDC 0078-0696-67
Entresto®
 (sacubitril/valsartan)
 tablets
97 mg/103 mg
 Rx only
 180 Tablets
 NOVARTIS

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

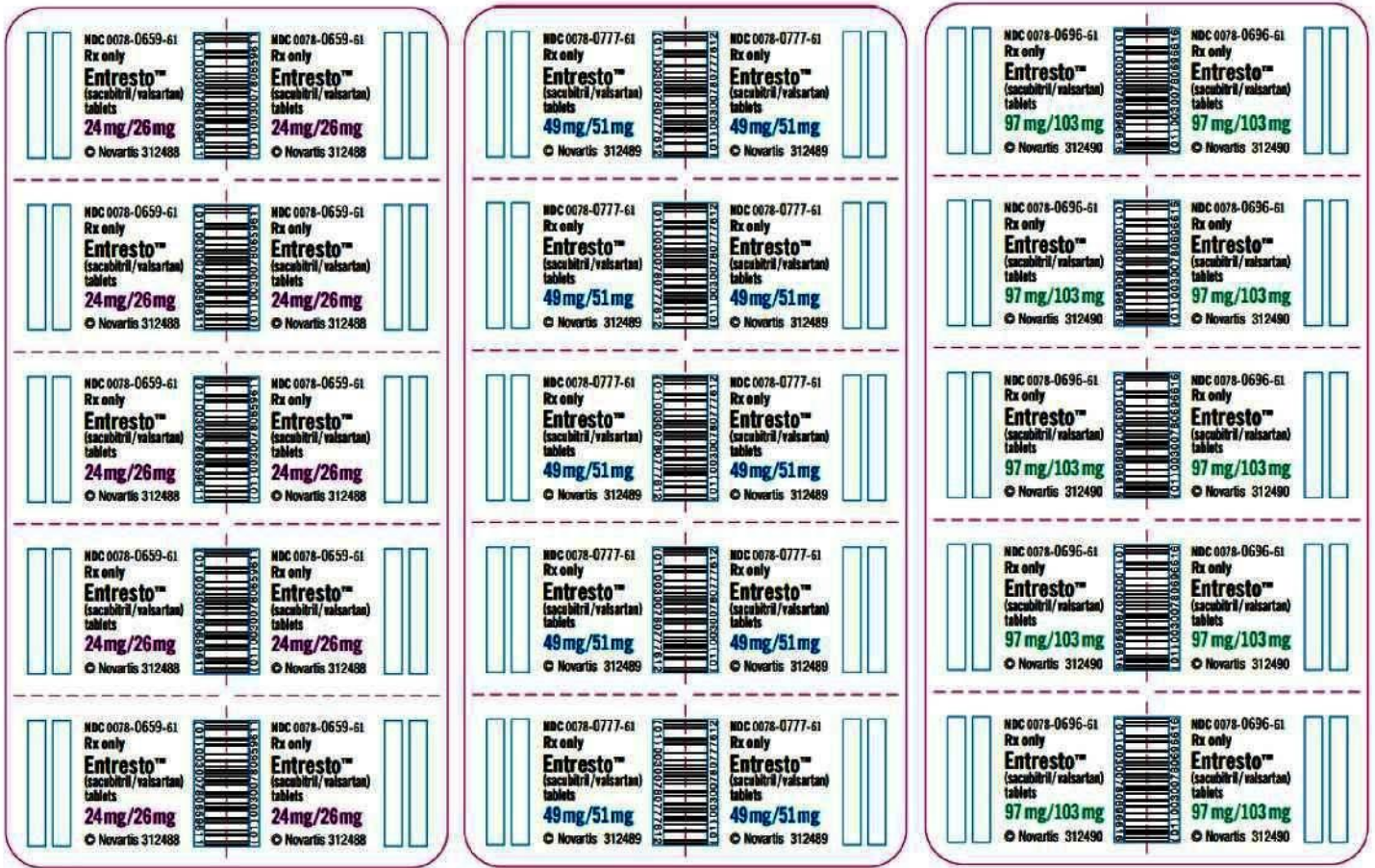


Model container/carton/blister labels (Source: DARRTS; ANRPT-3 submitted 8/30/2018). The RLD has delisted blister packs





Model container/carton/blister labels (Source: DARRTS; ANRPT-1 submitted 8/30/2016). The applicant is no longer marketing blisters container/cartons.



3.4 UNITED STATES PHARMACOPEIA (USP)

The USP was searched on 3/30/2020.

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		Click here to enter text.	Click here to enter text.
Not Yet Official	NO	Click here to enter the date when the monograph becomes official.	Click here to enter text.	Click here to enter text.

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:

NA

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 3/30/2020.

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 PED 05/27/2024			IV	7/8/2019	None
8101659	2023-01-14 Ped 7/14/2023			IV	7/8/2019	None
8404744	2023-01-14 PED 7/14/2023			IV	7/8/2019	None
8796331	2023-01-14 PED 7/14/2023	U-1723	TREATMENT OF HEART FAILURE	IV	7/8/2019	None
8877938	2027-05-27 PED 11/27/2027			IV	7/8/2019	None
9388134	2026-11-08 PED 05/08/2027	U-1723	TREATMENT OF HEART FAILURE	IV	7/8/2019	None

Reviewer Assessment:

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

Reviewer Comments:

NA

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	07/07/2020 PED 01/07/2021	NEW CHEMICAL ENTITY	does not intend to market prior to the expiration of the NCE exclusivity.	7/8/2019	None
NPP/S-013	10/02/2022 PED 04/01/2023	New Patient Population	does not intend to market prior to the expiration of the NPP exclusivity.	11/7/2019	None

Reviewer Assessment:

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

Reviewer Comments:

NA

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)? **YES**
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
(b)(4)	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 croscopovidone, low-substituted hydroxypropylcellulose, magnesium stearate, microcrystalline cellulose, and silicon dioxide. The film-coat inactive ingredients are hypromellose, titanium dioxide, Macrogol 4000, talc, and iron oxide red. 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. The film-coat for the 49 mg of sacubitril and 51 mg of valsartan tablet contains iron oxide yellow.	(b)(4)

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
Previous Labeling Review	Currently Proposed	Assessment

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

16 HOW SUPPLIED/STORAGE AND HANDLING Sacubitril and valsartan tablets are available as described below: Sacubitril and valsartan tablets 24/26 mg, (sacubitril 24 mg and valsartan 26 mg) are violet white color, oval shaped, biconvex film-coated tablets debossed with "S5" on one side and plain on the other side. Bottles of 30 NDC 42385-930-30 Bottles of 60 NDC 42385-930-60 Bottles of 180 NDC 42385-930-18 Carton with 100 (10 x 10) Unit-Dose Tablets containing cold form with desiccant blisters NDC 42385-930-68 Carton with 100 (10 x 10) Unit-Dose Tablets containing PVC/ACLAR blisters NDC 42385-930-72 Sacubitril and valsartan tablets 49/51 mg, (sacubitril 49 mg and valsartan 51 mg) are pale yellow color, oval shaped, biconvex film-coated tablets debossed with "S1" on one side and plain on the other side. Bottles of 30 NDC 42385-931-30 Bottles of 60 NDC 42385-931-60 Bottles of 180 NDC 42385-931-18 Carton with 100 (10 x 10) Unit-Dose Tablets containing cold form with desiccant blisters NDC 42385-931-68 Carton with 100 (10 x 10) Unit-Dose Tablets containing PVC/ACLAR blisters NDC 42385-931-72 Sacubitril and valsartan tablets 97/103 mg, (sacubitril 97 mg and valsartan 103 mg) are light pink color, oval shaped, biconvex film-coated tablets debossed with "S2" on one side and plain on the other side. Bottles of 30 NDC 42385-932-30 Bottles of 60 NDC 42385-932-60 Bottles of 180 NDC 42385-932-18 Carton with 100 (10 x 10) Unit-Dose Tablets containing cold form with desiccant blisters NDC 42385-932-68 Carton with 100 (10 x 10) Unit-Dose Tablets containing PVC/ACLAR blisters NDC 42385-932-72 Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature]. Protect from moisture.	16 HOW SUPPLIED/STORAGE AND HANDLING Sacubitril and valsartan tablets are available as described below: Sacubitril and valsartan tablets 24/26 mg, (sacubitril 24 mg and valsartan 26 mg) are violet white color, oval shaped, biconvex film-coated tablets debossed with "S5" on one side and plain on the other side. Bottles of 30 NDC 42385-930-30 Bottles of 60 NDC 42385-930-60 Bottles of 180 NDC 42385-930-18 Carton with 100 (10 x 10) Unit-Dose Tablets containing cold form with desiccant blisters NDC 42385-930-68 Carton with 100 (10 x 10) Unit-Dose Tablets containing PVC/ACLAR blisters NDC 42385-930-72 Sacubitril and valsartan tablets 49/51 mg, (sacubitril 49 mg and valsartan 51 mg) are pale yellow color, oval shaped, biconvex film-coated tablets debossed with "S1" on one side and plain on the other side. Bottles of 30 NDC 42385-931-30 Bottles of 60 NDC 42385-931-60 Bottles of 180 NDC 42385-931-18 Carton with 100 (10 x 10) Unit-Dose Tablets containing cold form with desiccant blisters NDC 42385-931-68 Carton with 100 (10 x 10) Unit-Dose Tablets containing PVC/ACLAR blisters NDC 42385-931-72 Sacubitril and valsartan tablets 97/103 mg, (sacubitril 97 mg and valsartan 103 mg) are light pink color, oval shaped, biconvex film-coated tablets debossed with "S2" on one side and plain on the other side. Bottles of 30 NDC 42385-932-30 Bottles of 60 NDC 42385-932-60 Bottles of 180 NDC 42385-932-18 Carton with 100 (10 x 10) Unit-Dose Tablets containing cold form with desiccant blisters NDC 42385-932-68 Carton with 100 (10 x 10) Unit-Dose Tablets containing PVC/ACLAR blisters NDC 42385-932-72 Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature]. Protect from moisture.	No change

Table 7: Manufacturer/Distributor/Packer Statements

Previous Labeling Review	Currently Proposed	Assessment
Manufactured for: Laurus Generics Inc. 400 Connell Drive Suite 5200 Berkeley Heights, NJ 07922 Manufactured by: Laurus Labs Limited Visakhapatnam-531011 India Revised: 06/2019	Manufactured for: Laurus Generics Inc. 400 Connell Drive Suite 5200 Berkeley Heights, NJ 07922 Manufactured by: Laurus Labs Limited Visakhapatnam-531011 India Revised: 11/2019	No change except revision date.

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:

NA

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 in 30s 60s and 180s count bottles)	11/7/2019	Satisfactory
Blister	Final	10s cold form and 10s pvc/aclar	11/7/2019	Satisfactory
Carton	Final	100s	11/7/2019	Satisfactory
(Other – specify)	NA	Click here to enter text.	Click here to enter text.	Click here to enter text.
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	Final	Revised: 11/2019	11/7/2019	Satisfactory
Medication Guide	NA			
Patient Information	Final	Revised: 11/2019	11/7/2019	Satisfactory
SPL Data Elements	1 st cycle-NA	Click here to enter text.	Click here to enter text.	Click here to enter text.



Angela
Payne

Digitally signed by Angela Payne
Date: 4/02/2020 02:06:05PM
GUID: 508da70600028ab611d2ba935d5074a6



Betty
Turner

Digitally signed by Betty Turner
Date: 4/02/2020 02:21:56PM
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	06/07/2021
ANDA Number(s)	213676
Review Number	3
Applicant Name	Laurus Labs 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	May 3, 2021
Primary Labeling Reviewer	Angela Payne
Secondary Labeling Reviewer	Marshall Florence
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 (C3)

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT (C3)

Labeling deficiencies based on your submission received May 3, 2021:

1. GENERAL COMMENTS

(b)(4)

2. CARTON LABELING

Unit-dose 100s (10x10)- To be consistent with the RLD's cartons, consider adding "For Institutional Use Only." statement.

3. PRESCRIBING INFORMATION

a. HIGHLIGHTS, INDICATIONS AND USAGE- Revise to read the same as the RLD.

i. First paragraph- (b)(4) "Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal."

ii. (b)(4)

b. HIGHLIGHTS, RECENT MAJOR CHANGES- Revise to read the same as the RLD labeling.

c. INDICATIONS AND USAGE- Revise to read the same as the RLD or provide a comment why you feel this information should not be included.

i. First paragraph- (b)(4) "Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal".

ii. (b)(4)

d. Clinical Trials, Section 6

Please ensure this section is up to date with the most recently approved RLD labeling posted at Drugs@FDA and is aligned with your patent certifications and exclusivity statements.

e. Clinical Trials Experience 6.1, Adult Heart Failure

(b)(4) This study was in the previously approved RLD labeling and your previous ANDA labeling submission. Any updates occurring in the recent approval to section 6.1 would also be retained.

(b)(4)

"In PARADIGM-HF, incidence of angioedema was 0.1% in both the enalapril and ENTRESTO run-in periods. In the double-blind period, the incidence of angioedema was higher in patients treated with ENTRESTO than enalapril (0.5% and 0.2%, respectively). The incidence of angioedema in Black patients was 2.4% with ENTRESTO and 0.5% with enalapril [see Warnings and Precautions (5.2)].

Orthostasis was reported in 2.1% of patients treated with ENTRESTO compared to 1.1% of patients treated with enalapril during the double-blind period of PARADIGM-HF. Falls were reported in 1.9% of patients treated with ENTRESTO compared to 1.3% of patients treated with enalapril.

4. PATIENT INFORMATION LEAFLET

(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 (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 (C3)

1.3 POST-APPROVAL REVISIONS (C3)

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

2 INSTRUCTIONS FOR ASSESSMENT (C3)

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.



3 OVERALL ASSESSMENT OF MATERIALS REVIEWED (C3)

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 in 30s, 60s, and 180s count bottles (b)(4)	11/7/2019	Satisfactory
Blister	Final	10s unit dose cold form and 10s pvc/aclar	11/7/2019	Satisfactory
Carton	Final	100s (10x10) unit dose	11/7/2019	Revise

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	4/2021	5/3/2021	Revise
Medication Guide	N/A	N/A		
Patient Information	Final	4/2021	5/3/2021	Revise
Instructions for Use	N/A	N/A		
SPL Data Elements				

4 LABELING REVIEW INFORMATION(C3)

4.1 REGULATORY INFORMATION (C3)

Yes	No	
☒	☐	Are there any applicable issues in DLR's SharePoint Drug Facts ? (b)(4)
☒	☐	Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint ? checked PAL#06042021 Request FDA to: (1) Review ANDAs that reference ENTRESTO to demonstrate API common; (2) Review FDA's Draft Guidance document regarding sacubitril/valsartan oral tablets to recommend that API commonness be established by showing that the chemical structures 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 salts/bands; (3) Further revise the Draft Guidance to include SE and PK requirements. CP: FDA-2019-P-189 Entresto sacubitril/valsartan tablets 202002 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.

4.2 MODEL PRESCRIBING INFORMATION (C3)

Table 3: Review Model Labeling for Prescribing Information/Patient Labeling (Check the box used as the Model Labeling)	
☒	MOST RECENTLY APPROVED NDA MODEL LABELING <i>(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.)</i> NDA#/Supplement# (S-000 if original): NDA207620 / S-018 Supplement Approval Date: 02/16/2021 Proprietary Name: Entresto Established Name: sacubitril/valsartan Description of Supplement: SE-018- approved 02/16/2021. 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. SE-013- approved 10/01/2019. 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 3: Review Model Labeling for Prescribing Information/Patient Labeling
(Check the box used as the Model Labeling)**

***OTHER IMPORTANT INFORMATION:**

- Supplement 16 (CBE-30 CMC supplement): (b)(4)

(b)(4)

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

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):

Reviewer Assessment:

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

Reviewer Comments:

It is noted by current reviewer that in the ANDA labeling, the updated paradigm trail information, added in S-018, was carved out by the applicant. (b)(4)

(b)(4)

Deficiency Comments:

Deficiency # 1

Created in C3

General Comments

(b)(4)

Response / Assessment:

4.3 PATENTS AND EXCLUSIVITIES (C3)

The [Orange Book](#) was searched on 06/07/2021

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 (enter Carve-out or None)
97MG;103MG, 49MG;51MG, 24MG;26MG	7468390*PED	05/27/2024			IV	7/8/2019	None
97MG;103MG, 49MG;51MG, 24MG;26MG	7468390	11/27/2023			IV	7/8/2019	None
97MG;103MG, 49MG;51MG, 24MG;26MG	8101659*PED	07/14/2023			IV	7/8/2019	None
49MG;51MG, 97MG;103MG, 24MG;26MG	8101659	01/14/2023			IV	7/8/2019	None
97MG;103MG, 49MG;51MG, 24MG;26MG	8404744*PED	07/14/2023			IV	7/8/2019	None
49MG;51MG, 24MG;26MG, 97MG;103MG	8404744	01/14/2023			IV	7/8/2019	None
97MG;103MG, 49MG;51MG, 24MG;26MG	8796331*PED	07/14/2023			IV	7/8/2019	None
49MG;51MG, 97MG;103MG, 24MG;26MG	8796331	01/14/2023	U-1723	TREATMENT OF HEART FAILURE	IV	7/8/2019	None
97MG;103MG, 49MG;51MG, 24MG;26MG	8877938*PED	11/27/2027			IV	7/8/2019	None
97MG;103MG, 49MG;51MG, 24MG;26MG	8877938	05/27/2027			IV	7/8/2019	None
97MG;103MG, 49MG;51MG, 24MG;26MG	9388134*PED	05/08/2027			IV	7/8/2019	None
24MG;26MG, 97MG;103MG, 49MG;51MG	9388134	11/08/2026	U-1723	TREATMENT OF HEART FAILURE	IV	7/8/2019	None
24MG;26MG, 49MG;51MG, 97MG;103MG	9517226	08/22/2033	U-3084	TREATMENT OF HEART FAILURE WITH PRESERVED EJECTION FRACTION	VIII	5/3/2021	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 (enter Carve-out or None)
24MG;26MG, 49MG;51MG, 97MG;103MG	9937143	08/22/2033	U-3084	TREATMENT OF HEART FAILURE WITH PRESERVED EJECTION FRACTION	VIII	5/3/2021	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 (enter Carve-out or None)
49MG;51MG, 97MG;103MG, 24MG;26MG	M-82	02/16/2024	LABELING REVISIONS RELATED TO CLINICAL STUDIES	will launch prior to expiry of M-82 exclusivity,	05/03/2021	Carve-out
97MG;103MG, 49MG;51MG, 24MG;26MG	NCE PED	01/07/2021	NEW CHEMICAL ENTITY; PEDIATRIC EXCLUSIVITY	does not intend to market prior to the expiration of the NCE exclusivity	07/08/2019	None
97MG;103MG, 49MG;51MG, 24MG;26MG	NPP PED	04/01/2023	NEW PATIENT POPULATION; PEDIATRIC EXCLUSIVITY	does not intend to market prior to the expiration of the NCE exclusivity	11/07/2019	None
49MG;51MG, 97MG;103MG, 24MG;26MG	NPP/S-013	10/01/2022	NEW PATIENT POPULATION	does not intend to market prior to the expiration of the NCE exclusivity. S-013	11/07/2019	None

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: MOU to Patent ...226' and 143' are new listing added based on S-018 recent approval that covered the Paragon-HF study and preserved ejection fraction. carve out of Exclusivity M-82 was granted for S-018 related to the paragon HF study.		
Deficiency Comments:		

4.4 UNITED STATES PHARMACOPEIA (USP) (C3)

The USP was searched on 06/07/2021

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:		
Deficiency Comments:		

4.5 MODEL CONTAINER LABELS (C3)

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



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.
Mfg. 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 0078-9050-50 121132 US5

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.
Mfg. 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

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.
Mfg. 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

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.
Mfg. 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 US5

NDC 0078-0777-20

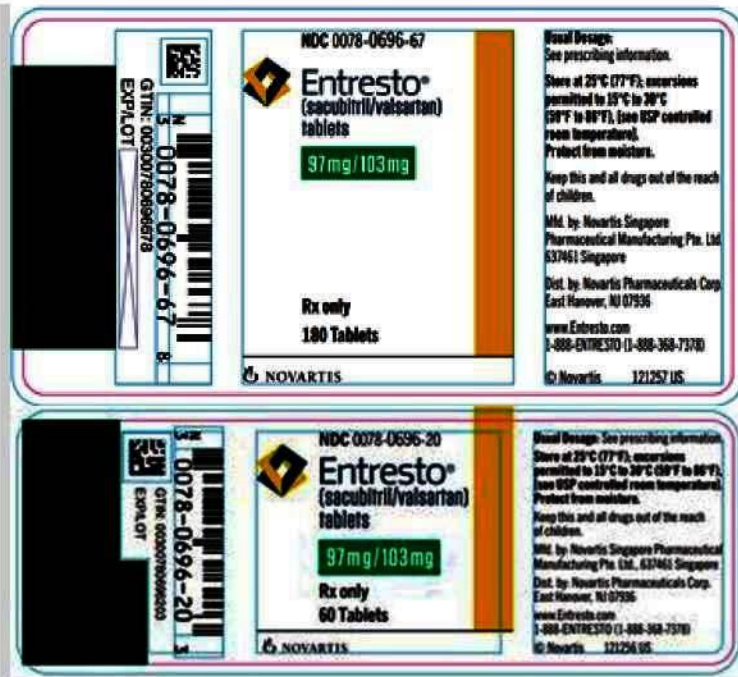
Entresto®
(sacubitril/valsartan)
tablets

49mg/51mg

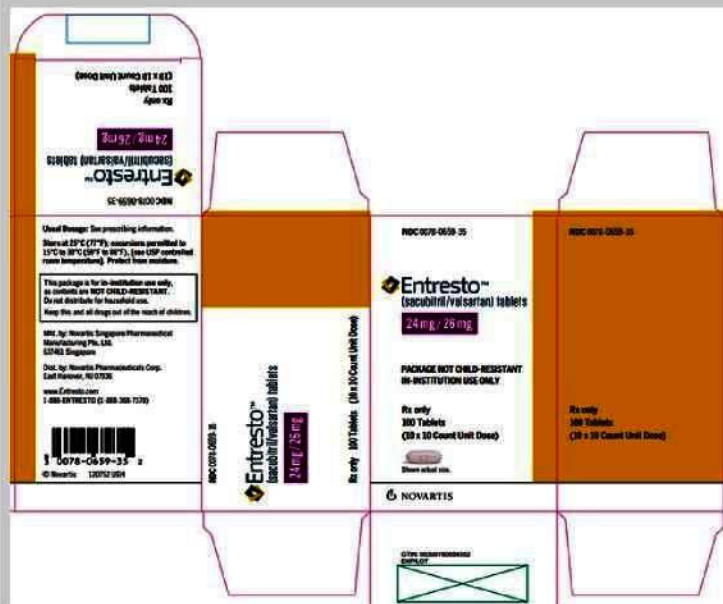
Rx only 60 Tablets

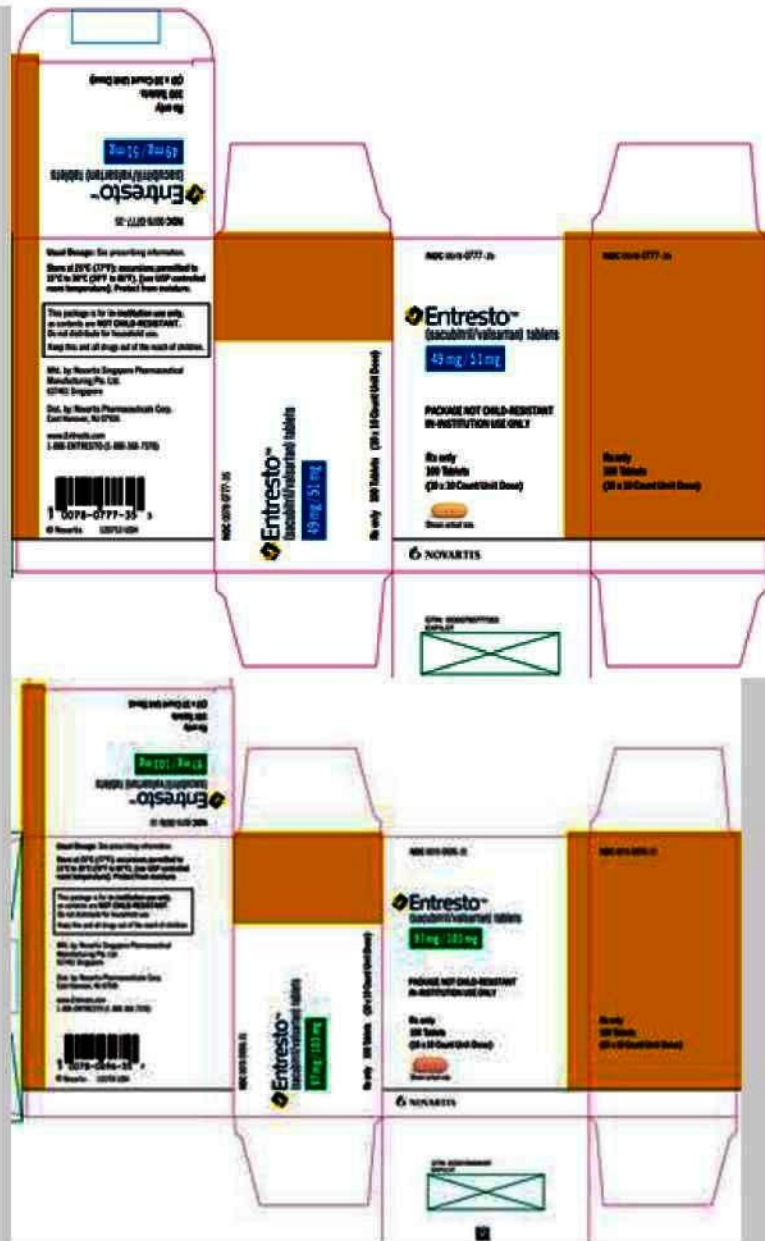
NOVARTIS

Usual Dosage: See prescribing information.
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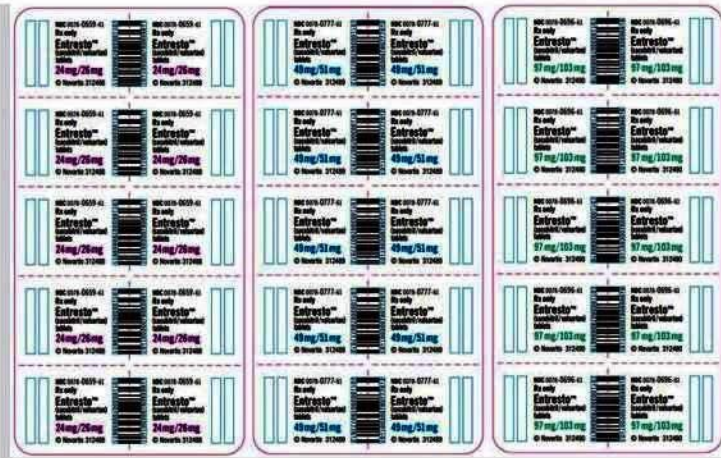


Model container/carton/blister labels (Source: DARRTS; ANRPT-3 submitted 8/30/2018). The RLD has delisted blister packs





Model container/carton/blister labels (Source: DARRTS; ANRPT-1 submitted 8/30/2016). The applicant is no longer marketing blisters container/cartons.



5 ASSESSMENT OF ANDA LABELING AND LABELS (C3)

5.1 QUALITY INFORMATION (DRUG PRODUCT MOU & BIOPHARMACEUTICS) (C3)

5.1.1 DRUG PRODUCT REVIEW (C3)

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

NA for Third cycle.

5.1.2 DESCRIPTION (C3)

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

Model Labeling	NA on 3rd cycle
ANDA Labeling	11 DESCRIPTION Sacubitril and valsartan tablets are a combination of a neprilysin inhibitor and an angiotensin II receptor blocker. Sacubitril and valsartan tablets contain a complex comprised of anionic forms of sacubitril and valsartan, and sodium cations in the molar ratio of 1:1:3, respectively. Following oral administration, the complex dissociates into sacubitril (which is further metabolized to LBQ657) and valsartan. The complex is chemically described as Tri sodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate]. Its molecular formula is C₄₈H₅₅N₆O₈•3Na. Its molecular mass is 912.95 and its schematic structural formula is: 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 crospovidone, low-substituted

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

	hydroxypropylcellulose, magnesium stearate, microcrystalline cellulose, and silicon dioxide. The film-coat inactive ingredients are hypromellose, titanium dioxide, Macrogol 4000, talc, and iron oxide red. 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. The film-coat for the 49 mg of sacubitril and 51 mg of valsartan tablet contains iron oxide yellow. Sacubitril Valsartan Structure

5.1.3 HOW SUPPLIED/STORAGE AND HANDLING (C3)

Table 8: Comparison of Model Labeling to ANDA Labeling

Model Labeling	NA to the third cycle review.
ANDA Labeling	16 HOW SUPPLIED/STORAGE AND HANDLING Sacubitril and valsartan tablets are available as described below: Sacubitril and valsartan tablets 24/26 mg, (sacubitril 24 mg and valsartan 26 mg) are violet white color, oval shaped, biconvex film-coated tablets debossed with “S5” on one side and plain on the other side. Bottles of 30 NDC 42385-930-30 Bottles of 60 NDC 42385-930-60 Bottles of 180 NDC 42385-930-18 Carton with 100 (10 x 10) Unit-Dose Tablets containing cold form with desiccant blisters NDC 42385-930-68 Carton with 100 (10 x 10) Unit-Dose Tablets containing PVC/ACLAR blisters NDC 42385-930-72 Sacubitril and valsartan tablets 49/51 mg, (sacubitril 49 mg and valsartan 51 mg) are pale yellow color, oval shaped, biconvex film-coated tablets debossed with “S1” on one side and plain on the other side. Bottles of 30 NDC 42385-931-30 Bottles of 60 NDC 42385-931-60 Bottles of 180 NDC 42385-931-18 Carton with 100 (10 x 10) Unit-Dose Tablets containing cold form with desiccant blisters NDC 42385-931-68 Carton with 100 (10 x 10) Unit-Dose Tablets containing PVC/ACLAR blisters NDC 42385-931-72 Sacubitril and valsartan tablets 97/103 mg, (sacubitril 97 mg and valsartan 103 mg) are light pink color, oval shaped, biconvex film-coated tablets debossed with “S2” on one side and plain on the other side. Bottles of 30 NDC 42385-932-30 Bottles of 60 NDC 42385-932-60 Bottles of 180 NDC 42385-932-18 Carton with 100 (10 x 10) Unit-Dose Tablets containing cold form with desiccant blisters NDC 42385-932-68 Carton with 100 (10 x 10) Unit-Dose Tablets containing PVC/ACLAR blisters NDC 42385-932-72 Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature]. Protect from moisture.

5.1.4 MANUFACTURER, DISTRIBUTOR, AND/OR PACKER(C3)

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

Name and Address of ANDA Manufacturer/Distributor/Packer (cite source as applicable)	(b)(4)

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

Name and Address on ANDA Container/Carton	(b) (4)
Name and Address on ANDA Prescribing Information	

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

Manufactured by	Manufactured for	Distributed by	Distributed for
(b)(4)	Manufactured for: Laurus Generics Inc. 400 Connell Drive Suite 5200 Berkeley Heights, NJ 07922 Revised: 04/2021		

5.2 CONTAINER LABEL (FOR BLISTERS GO TO UNIT-DOSE BLISTERS) (C3)

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.].
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.

Deficiency	No Deficiency	
☐	☒	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: Container labels found satisfactory during cycle 2. Carton labels had one post approval comment that we will relay to the applicant during cycle 3.		
Deficiency Comments:		

5.3 PRESCRIBING INFORMATION (C3)

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 enter Reviewer/Deficiency Comments if you select Deficiency.

Deficiency	No 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 <u>21 CFR 314.94(a)(8)</u> . Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

1. (b)(4)

2. (b)(4)

(b)(4) sentence to read as follows: "A total of 6,622 heart failure patients were treated with in the clinical trials. Of these, 5,085 were exposed for at least 1 year, (b)(4)"

(b)(4)

FTR:

(b)(4)

RLD I&U section from S-018

1.1 Adult Heart Failure

ENTRESTO is indicated 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 [see Clinical Studies (14.1)].

RLD i&U section from S-013, INDICATIONS AND USAGE

1.1 Adult Heart Failure

ENTRESTO 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.
ENTRESTO is usually administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other ARB.

Deficiency Comments:

Deficiency # 1

HIGHLIGHTS, INDICATIONS AND USAGE- Revise to read the same as the RLD.

Created in C3

Prescribing Information

(b)(4) “Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal.”

(b)(4)

Response / Assessment:

Deficiency # 2

HIGHLIGHTS, RECENT MAJOR CHANGES- Revise to read the same as the RLD labeling.

Created in C3

Prescribing Information

Response / Assessment:

Deficiency # 3

INDICATIONS AND USAGE- Revise to read the same as the RLD or provide a comment why you feel this information should not be included.

Created in C3

Prescribing Information

(b)(4) “Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal”.

(b)(4)

Response / Assessment:

Deficiency # 4

Clinical Trials, Section 6

Created in C3

Prescribing Information

Please ensure this section is up to date with the most recently approved RLD labeling posted at Drugs@FDA and is aligned with your patent certifications and exclusivity statements.

Response / Assessment:

Deficiency # 5	Clinical Trials Experience 6.1, Adult Heart Failure
Created in C3	(b)(4) This study was in the
Prescribing Information	previously approved RLD labeling and your previous ANDA labeling submission. Any updates occurring in the recent approval to section 6.1 would also be retained.
	(b)(4)
	"In PARADIGM-HF, incidence of angioedema was 0.1% in both the enalapril and ENTRESTO run-in periods. In the double-blind period, the incidence of angioedema was higher in patients treated with ENTRESTO than enalapril (0.5% and 0.2%, respectively). The incidence of angioedema in Black patients was 2.4% with ENTRESTO and 0.5% with enalapril [see Warnings and Precautions (5.2)].
	Orthostasis was reported in 2.1% of patients treated with ENTRESTO compared to 1.1% of patients treated with enalapril during the double-blind period of PARADIGM-HF. Falls were reported in 1.9% of patients treated with ENTRESTO compared to 1.3% of patients treated with enalapril.
Response / Assessment:	
Deficiency # 6	(b)(4)
Created in C3	
Patient Information Leaflet	
Response / Assessment:	
Deficiency # 7	Unit-dose 100s (10x10)- To be consistent with the RLD's cartons, consider adding "For Institutional Use Only." statement.
Created in C3	
Carton Labeling	
Response / Assessment:	

6 COMMENTS/CONSULTS FOR OTHER DISCIPLINES (C3)

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: NA	
Deficiency Comments:	



Angela
Payne

Digitally signed by Angela Payne
Date: 8/17/2021 03:38:08PM
GUID: 508da70600028ab611d2ba935d5074a6



Marshall
Florence

Digitally signed by Marshall Florence
Date: 8/18/2021 09:48:52AM
GUID: 55eefa420051b501ac3ced124279f785

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	12/01/2021
ANDA Number(s)	213676
Review Number	4
Applicant Name	Laurus Labs 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	N/A
Submission Received Date	November 26, 2021
Primary Labeling Reviewer	Angela Payne
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 (C4)

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

Labeling deficiencies based on your submission received November 26, 2021:

1. GENERAL COMMENTS

- a. GENERAL: Address the new information (or new patents/exclusivities) listed in the Orange Book for the reference listed drug (RLD), NDA 207620. Additionally, ensure all patent certifications and exclusivity statements are congruent among themselves and with the proposed labeling.
- b. GENERAL: Address patent number(s), 11135192 and 11058667 as listed in the "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book").

2. PRESCRIBING INFORMATION

a. HIGHLIGHTS

i. RECENT MAJOR CHANGES

We acknowledge your comment regarding the HIGHLIGHTS, RECENT MAJOR CHANGES request. However, please revise to read the same as the RLD labeling. Please note below, revisions for section 1.1.

ii. INDICATIONS AND USAGE

(b)(4)

- b. PRESCRIBING INFORMATION, INDICATIONS AND USAGE, Revise Section 1.1 Adult Heart Failure as follows:

(b)(4)

(b)(4) (LVEF) is a variable measure, so use clinical judgment in deciding whom to treat [see Clinical Studies (14.1)].

(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 (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 software interface for managing deficiency comments. It features a table with the following columns: 'Creation Cycle', 'Category', 'Deficiency', 'Response/Assessment', and 'Post-Approval'. The 'Creation Cycle' column contains the value 'C1'. The 'Category' column has a dropdown menu with the text '- Select -'. The 'Deficiency' column contains a rich text editor with various formatting options (bold, italic, underline, link, etc.). The 'Post-Approval' column contains a checkbox that is currently unchecked. A red arrow points from the 'Deficiency' column towards the 'Post-Approval' checkbox, and the checkbox itself is highlighted with a red rectangular box.

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 in 30s, 60s, and 180s count bottles (b)(4)	11/7/2019	Satisfactory
Blister	Final	10s unit dose cold form and 10s pvc/aclar	11/7/2019	Satisfactory
Carton	Final	100s (10x10) unit dose	11/26/21	Satisfactory

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	11/21	11/26/21	Revise
Medication Guide	N/A			
Patient Information	Final	11/21	11/26/21	Satisfactory
Instructions for Use	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)
☒	☐	Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint ? checked PAL#06042021 CP (FDA-2019-P-082) Events available selection labels 202002 Requests FDA to: (1) Review NDAs that reference ENTRESTO to demonstrate API common; (2) Review FDA's Draft Guidance document regarding combination and solids to assessment that API commonness is 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 salts/bands; (3) Further revise the Draft Guidance to include BE and PK requirements.
		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

4.2 MODEL PRESCRIBING INFORMATION (C4)

**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

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

Supplement Approval Date: 02/16/2021

Proprietary Name: Entresto Tablets

Established Name: sacubitril/valsartan tablets

Description of Supplement:

SE-018- approved 02/16/2021. 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.

SE-013- approved 10/01/2019. 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 16 (CBE-30 CMC supplement): PENDING; (b)(4)

(b)(4)

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

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)

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 PATENTS AND EXCLUSIVITIES (C4)

The Orange Book was searched on 06/07/2021

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 (enter Carve-out or None)
97MG;103MG, 49MG;51MG, 24MG;26MG	7468390*PED	05/27/2024			IV	7/8/2019	None
97MG;103MG, 49MG;51MG, 24MG;26MG	7468390	11/27/2023			IV	7/8/2019	None
97MG;103MG, 49MG;51MG, 24MG;26MG	8101659*PED	07/14/2023			IV	7/8/2019	None
49MG;51MG, 97MG;103MG, 24MG;26MG	8101659	01/14/2023			IV	7/8/2019	None
97MG;103MG, 49MG;51MG, 24MG;26MG	8404744*PED	07/14/2023			IV	7/8/2019	None
49MG;51MG, 24MG;26MG, 97MG;103MG	8404744	01/14/2023			IV	7/8/2019	None
97MG;103MG, 49MG;51MG, 24MG;26MG	8796331*PED	07/14/2023			IV	7/8/2019	None
49MG;51MG, 97MG;103MG, 24MG;26MG	8796331	01/14/2023	U-1723	TREATMENT OF HEART FAILURE	IV	7/8/2019	None
97MG;103MG, 49MG;51MG, 24MG;26MG	8877938*PED	11/27/2027			IV	7/8/2019	None
97MG;103MG, 49MG;51MG, 24MG;26MG	8877938	05/27/2027			IV	7/8/2019	None
97MG;103MG, 49MG;51MG, 24MG;26MG	9388134*PED	05/08/2027			IV	7/8/2019	None
24MG;26MG, 97MG;103MG, 49MG;51MG	9388134	11/08/2026	U-1723	TREATMENT OF HEART FAILURE	IV	7/8/2019	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 (enter Carve-out or None)
24MG;26MG, 49MG;51MG, 97MG;103MG	9517226	08/22/2033	U-3084	TREATMENT OF HEART FAILURE WITH PRESERVED EJECTION FRACTION	VIII	5/3/2021	Carve-out
24MG;26MG, 49MG;51MG, 97MG;103MG	9937143	08/22/2033	U-3084	TREATMENT OF HEART FAILURE WITH PRESERVED EJECTION FRACTION	VIII	5/3/2021	Carve-out
24MG;26MG, 49MG;51MG, 97MG;103MG	11135192	08/22/2033	U-3084	TREATMENT OF HEART FAILURE WITH PRESERVED EJECTION FRACTION			Missing
24MG;26MG, 49MG;51MG, 97MG;103MG	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			Missing

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 (enter Carve-out or None)
49MG;51MG, 97MG;103MG, 24MG;26MG	M-82	02/16/2024	LABELING REVISIONS RELATED TO CLINICAL STUDIES	will launch prior to expiry of M-82 exclusivity,	05/03/2021	Carve-out
97MG;103MG, 49MG;51MG, 24MG;26MG	NCE PED	01/07/2021	NEW CHEMICAL ENTITY; PEDIATRIC EXCLUSIVITY	does not intend to market prior to the expiration of the NCE exclusivity	07/08/2019	None
97MG;103MG, 49MG;51MG, 24MG;26MG	NPP PED	04/01/2023	NEW PATIENT POPULATION; PEDIATRIC EXCLUSIVITY	does not intend to market prior to the expiration of the NCE exclusivity	11/07/2019	None
49MG;51MG, 97MG;103MG, 24MG;26MG	NPP/S-013	10/01/2022	NEW PATIENT POPULATION	does not intend to market prior to the expiration of the NCE exclusivity. S-013	11/07/2019	None

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

GENERAL: Address the new information (or new patents/exclusivities) listed in the Orange Book for the reference listed drug (RLD), NDA 207620. Additionally, ensure all patent certifications and exclusivity statements are congruent among themselves and with the proposed labeling.

GENERAL: Address patent number(s), 11135192 and 11058667 as listed in the "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book").

Response / Assessment:

4.4 UNITED STATES PHARMACOPEIA (USP) (C4)

The USP was searched on 12/01/2021

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 (C4)

Model container/carton/blister labels (Source: labels (Source: DARRTS; S-016, approved 2/20/2020) (b)(4))

Physician Sample
Not for Sale

Entresto
(sacubitril/valsartan)
tablets

24 mg/26 mg

Rx only
28 Tablets

NOVARTIS

1825772 USS

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.
Mfg. 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

NDC 0078-0777-67

Entresto
(sacubitril/valsartan)
tablets

49 mg/51 mg

Rx only
180 Tablets

NOVARTIS

1826200 US

0078-0777-67

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.
Mfg. 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

NDC 0078-0696-20

Entresto
(sacubitril/valsartan)
tablets

97 mg/103 mg

Rx only
60 Tablets

NOVARTIS

1826201 US

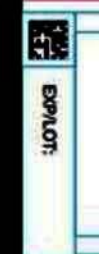
0078-0696-20

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.
Mfg. 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

DARRTS; ANRPT-4 submitted 8/30/2019. Note storage is not updated per S-016.


NDC 0078-0659-67
Entresto®
 (sacubitril/valsartan)
 tablets
24 mg/26 mg
 Rx only
 180 Tablets


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.
 Mfg. 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 121253 US

**Physician Sample
 Not for Sale**

NDC 0078-0659-67
Entresto®
 (sacubitril/valsartan)
 tablets
24 mg/26 mg
 Rx only 28 Tablets


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.
 Mfg. 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 0078-9009-50 12112 US


NDC 0078-0659-20
Entresto®
 (sacubitril/valsartan)
 tablets
24 mg/26 mg
 Rx only
 60 Tablets


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.
 Mfg. 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


NDC 0078-0777-67
Entresto®
 (sacubitril/valsartan)
 tablets
49 mg/51 mg
 Rx only
 180 Tablets


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.
 Mfg. 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

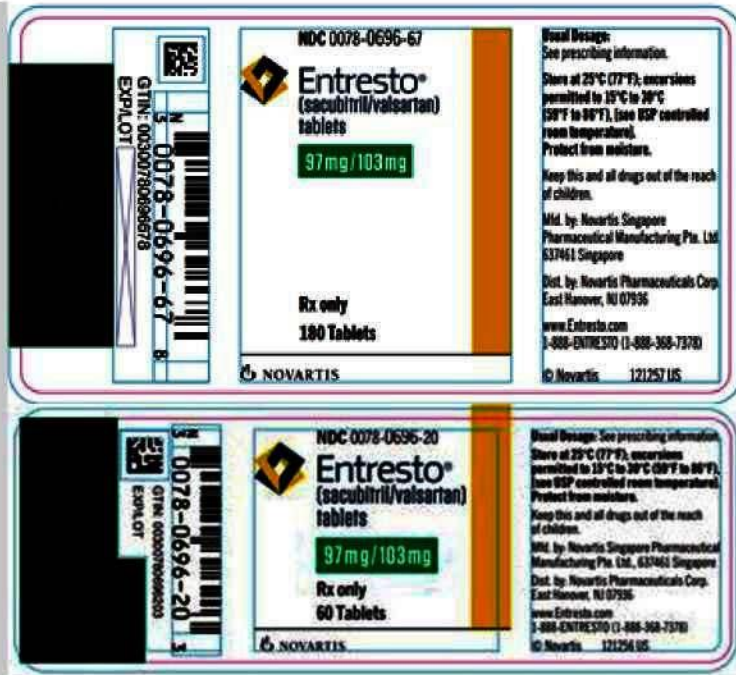
**Physician Sample
 Not for Sale**

NDC 0078-0777-67
Entresto®
 (sacubitril/valsartan)
 tablets
49 mg/51 mg
 Rx only 28 Tablets


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.
 Mfg. 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 0078-5777-50 121138 US


NDC 0078-0777-20
Entresto®
 (sacubitril/valsartan)
 tablets
49 mg/51 mg
 Rx only
 60 Tablets


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.
 Mfg. 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



Model container/carton/blister labels (Source: DARRTS; ANRPT-3 submitted 8/30/2018). The RLD has delisted blister packs

24 mg / 26 mg

Entresto™ (sacubitril/valsartan) tablets

NDC 0719-0259-35

Usual Dosage: See prescribing information. Store at 20°C (67°F); excursions permitted to 15°C to 30°C (59°F to 86°F) (see USP controlled room temperature). Protect from moisture.

This package is for in-hospital use only, as contents are NOT CHILD-RESISTANT. Do not distribute for household use. Keep the cap and all of the cap out of the reach of children.

Mfg. by Novartis Singapore Pharmaceutical Manufacturing Pte. Ltd. 627612 Singapore

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

www.entresto.com
1-800-492-9525 • 1-800-848-7170

1 357-690-22-2

© Novartis 13752-0259

NDC 0719-0259-35

Entresto™ (sacubitril/valsartan) tablets
24 mg / 26 mg

Rx only 300 Tablets (30 x 10-Count Unit Dose)

NDC 0719-0259-35

Entresto™ (sacubitril/valsartan) tablets
24 mg / 26 mg

Rx only 300 Tablets (30 x 10-Count Unit Dose)

PACKAGE NOT CHILD-RESISTANT IN INSTITUTION USE ONLY

Rx only 300 Tablets (30 x 10-Count Unit Dose)

NOVARTIS

49 mg / 51 mg

Entresto™ (sacubitril/valsartan) tablets

NDC 0719-0777-35

Usual Dosage: See prescribing information. Store at 20°C (67°F); excursions permitted to 15°C to 30°C (59°F to 86°F) (see USP controlled room temperature). Protect from moisture.

This package is for in-hospital use only, as contents are NOT CHILD-RESISTANT. Do not distribute for household use. Keep the cap and all of the cap out of the reach of children.

Mfg. by Novartis Singapore Pharmaceutical Manufacturing Pte. Ltd. 627612 Singapore

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

www.entresto.com
1-800-492-9525 • 1-800-848-7170

1 357-777-8100

© Novartis 13752-0777

NDC 0719-0777-35

Entresto™ (sacubitril/valsartan) tablets
49 mg / 51 mg

Rx only 300 Tablets (30 x 10-Count Unit Dose)

NDC 0719-0777-35

Entresto™ (sacubitril/valsartan) tablets
49 mg / 51 mg

Rx only 300 Tablets (30 x 10-Count Unit Dose)

PACKAGE NOT CHILD-RESISTANT IN INSTITUTION USE ONLY

Rx only 300 Tablets (30 x 10-Count Unit Dose)

NOVARTIS

113 mg / 133 mg

Entresto™ (sacubitril/valsartan) tablets

NDC 0719-0261-35

Usual Dosage: See prescribing information. Store at 20°C (67°F); excursions permitted to 15°C to 30°C (59°F to 86°F) (see USP controlled room temperature). Protect from moisture.

This package is for in-hospital use only, as contents are NOT CHILD-RESISTANT. Do not distribute for household use. Keep the cap and all of the cap out of the reach of children.

Mfg. by Novartis Singapore Pharmaceutical Manufacturing Pte. Ltd. 627612 Singapore

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

www.entresto.com
1-800-492-9525 • 1-800-848-7170

1 357-654-21-3

© Novartis 13752-0261

NDC 0719-0261-35

Entresto™ (sacubitril/valsartan) tablets
113 mg / 133 mg

Rx only 300 Tablets (30 x 10-Count Unit Dose)

NDC 0719-0261-35

Entresto™ (sacubitril/valsartan) tablets
113 mg / 133 mg

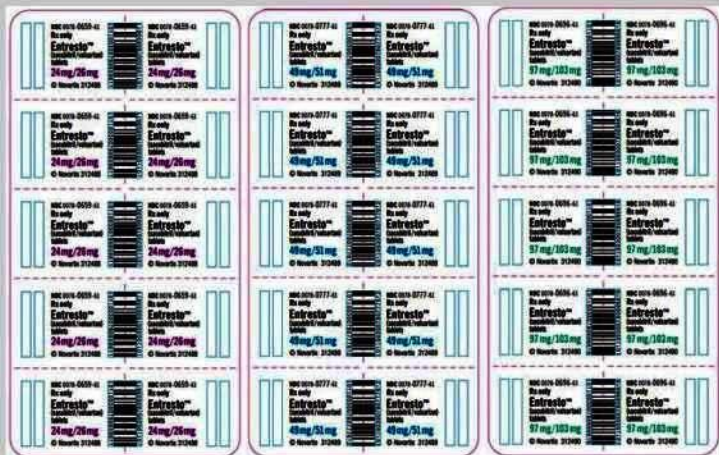
Rx only 300 Tablets (30 x 10-Count Unit Dose)

PACKAGE NOT CHILD-RESISTANT IN INSTITUTION USE ONLY

Rx only 300 Tablets (30 x 10-Count Unit Dose)

NOVARTIS

Model container/carton/blister labels (Source: DARRTS; ANRPT-1 submitted 8/30/2016). The applicant is no longer marketing blisters container/cartons.



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

R03, 9/22/2021

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	Dimension (mm) (Length x Width)	Imprint Code
24mg/26mg	9.11x 5.08	Violet white color, oval, biconvex film-coated tablets debossed with "S5" on one side and plain on the other side.
49mg/51mg	12.75 x 5.90	Pale yellow color, oval, biconvex film-coated tablets debossed with "S1" on one side and plain on the other side.
97mg/103mg	12.57 x 6.85	Light pink color, oval, biconvex film-coated tablets debossed with "S2" on one side and plain on the other side.

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 (C4)

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

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

	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	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 crospovidone, low-substituted hydroxypropylcellulose, magnesium stearate, microcrystalline cellulose, and silicon dioxide. The film-coat inactive ingredients are hypromellose, titanium dioxide, Macrogol 4000, talc, and iron oxide red. 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. The film-coat for the 49 mg of sacubitril and 51 mg of valsartan tablet contains iron oxide yellow.
Current 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 crospovidone, low-substituted hydroxypropylcellulose, magnesium stearate, microcrystalline cellulose, and silicon dioxide. The film-coat inactive ingredients are hypromellose, titanium dioxide, Macrogol 4000, talc, and iron oxide red. 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. The film-coat for the 49 mg of sacubitril and 51 mg of valsartan tablet contains iron oxide yellow.

5.1.3 HOW SUPPLIED/STORAGE AND HANDLING (C4)

Table 8: Comparison of Model Labeling to ANDA Labeling

Model Labeling	16 HOW SUPPLIED/STORAGE AND HANDLING 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 border="1"> <thead> <tr> <th>Tablet</th> <th>Color</th> <th>Debossment</th> <th colspan="2">NDC # 0078-XXXX-XX</th> </tr> <tr> <th>Sacubitril/Valsartan</th> <th></th> <th>"NVR" and</th> <th>Bottle of 60</th> <th>Bottle of 180</th> </tr> </thead> <tbody> <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> </tbody> </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	16 HOW SUPPLIED/STORAGE AND HANDLING Sacubitril and valsartan tablets are available as described below: Sacubitril and valsartan tablets 24/26 mg, (sacubitril 24 mg and valsartan 26 mg) are violet white color, oval shaped, biconvex film-coated tablets debossed with "S5" on one side and plain on the other side. Bottles of 30 NDC 42385-930-30 Bottles of 60 NDC 42385-930-60 Bottles of 180 NDC 42385-930-18 Carton with 100 (10 x 10) Unit-Dose Tablets containing cold form with desiccant blisters NDC																									

Table 8: Comparison of Model Labeling to ANDA Labeling

	42385-930-68 Carton with 100 (10 x 10) Unit-Dose Tablets containing PVC/ACLAR blisters NDC 42385-930-72 Sacubitril and valsartan tablets 49/51 mg, (sacubitril 49 mg and valsartan 51 mg) are pale yellow color, oval shaped, biconvex film-coated tablets debossed with “S1” on one side and plain on the other side. Bottles of 30 NDC 42385-931-30 Bottles of 60 NDC 42385-931-60 Bottles of 180 NDC 42385-931-18 Carton with 100 (10 x 10) Unit-Dose Tablets containing cold form with desiccant blisters NDC 42385-931-68 Carton with 100 (10 x 10) Unit-Dose Tablets containing PVC/ACLAR blisters NDC 42385-931-72 Sacubitril and valsartan tablets 97/103 mg, (sacubitril 97 mg and valsartan 103 mg) are light pink color, oval shaped, biconvex film-coated tablets debossed with “S2” on one side and plain on the other side. Bottles of 30 NDC 42385-932-30 Bottles of 60 NDC 42385-932-60 Bottles of 180 NDC 42385-932-18 Carton with 100 (10 x 10) Unit-Dose Tablets containing cold form with desiccant blisters NDC 42385-932-68 Carton with 100 (10 x 10) Unit-Dose Tablets containing PVC/ACLAR blisters NDC 42385-932-72 Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature]. Protect from moisture.
Current ANDA Labeling	16 HOW SUPPLIED/STORAGE AND HANDLING Sacubitril and valsartan tablets are available as described below: Sacubitril and valsartan tablets 24/26 mg, (sacubitril 24 mg and valsartan 26 mg) are violet white color, oval shaped, biconvex film-coated tablets debossed with “S5” on one side and plain on the other side. Bottles of 30 NDC 42385-930-30 Bottles of 60 NDC 42385-930-60 Bottles of 180 NDC 42385-930-18 Carton with 100 (10 x 10) Unit-Dose Tablets containing cold form with desiccant blisters NDC 42385-930-68 Carton with 100 (10 x 10) Unit-Dose Tablets containing PVC/ACLAR blisters NDC 42385-930-72 Sacubitril and valsartan tablets 49/51 mg, (sacubitril 49 mg and valsartan 51 mg) are pale yellow color, oval shaped, biconvex film-coated tablets debossed with “S1” on one side and plain on the other side. Bottles of 30 NDC 42385-931-30 Bottles of 60 NDC 42385-931-60 Bottles of 180 NDC 42385-931-18 Carton with 100 (10 x 10) Unit-Dose Tablets containing cold form with desiccant blisters NDC 42385-931-68 Carton with 100 (10 x 10) Unit-Dose Tablets containing PVC/ACLAR blisters NDC 42385-931-72 Sacubitril and valsartan tablets 97/103 mg, (sacubitril 97 mg and valsartan 103 mg) are light pink color, oval shaped, biconvex film-coated tablets debossed with “S2” on one side and plain on the other side. Bottles of 30 NDC 42385-932-30 Bottles of 60 NDC 42385-932-60 Bottles of 180 NDC 42385-932-18 Carton with 100 (10 x 10) Unit-Dose Tablets containing cold form with desiccant blisters NDC 42385-932-68 Carton with 100 (10 x 10) Unit-Dose Tablets containing PVC/ACLAR blisters NDC 42385-932-72

Table 8: Comparison of Model Labeling to ANDA Labeling

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

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	(b)(4)
Current ANDA Labeling	
Name and Address on ANDA Prescribing Information	(b)(4)

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

Manufactured by	Manufactured for	Distributed by	Distributed for
(b)(4)	Manufactured for: Laurus Generics Inc. 400 Connell Drive Suite 5200 Berkeley Heights, NJ 07922 Revised: 11/2021		

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

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.].
PRODUCT DIFFERENTIATION:		

Deficiency	No Deficiency	
☐	☒	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)].
☐	☒	<u>Tamper evident (controlled substances)</u> 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: Container labels found satisfactory during cycle 2.		
Deficiency Comments:		

5.2.1 UNIT-DOSE BLISTERS(C4)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Each blister contains only one dosage unit (e.g. one tablet, one capsule).
☐	☒	Established/proprietary name, strength, bar code, and manufacturer/distributor/packer appear accurately on each blister cell.
Reviewer Comments: Satisfactory in the previous cycle 2.		
Deficiency Comments:		

5.3 CARTON (OUTER OR SECONDARY PACKAGING) LABELING (C4)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	The answers to the Container Label questions are the same for the Carton Labeling. Please enter Reviewer/Deficiency Comments if you select Deficiency.
Reviewer Comments: U/D carton labels are satisfactory in the 11/26/2021 submission.		
Deficiency Comments:		

5.4 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 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)

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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.

(b)(4)

Deficiency Comments:

Deficiency # 1

HIGHLIGHTS, INDICATIONS AND USAGE- Revise to read the same as the RLD.

Created in C3

Prescribing Information

First paragraph- (b)(4) "Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal".

(b)(4)

Studies (14.1).

Response / Assessment:

(b)(4) This is acceptable.

(b)(4)

Deficiency # 2

HIGHLIGHTS, RECENT MAJOR CHANGES- Revise to read the same as the RLD labeling.

Created in C3

Prescribing Information

Response / Assessment:

Addressed adequately in the 11/26/2021 submission.

Deficiency # 3

INDICATIONS AND USAGE- Revise to read the same as the RLD or provide a comment why you feel this information should not be included.

Created in C3

Prescribing Information

First paragraph- (b)(4) "Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal".

(b)(4)

Response / Assessment:

Deficiency # 4

Clinical Trials, Section 6

Created in C3

Prescribing Information
Please ensure this section is up to date with the most recently approved RLD labeling posted at Drugs@FDA and is aligned with your patent certifications and exclusivity statements.

Response / Assessment: applicant addressed this comment in the 11/26/2021 submission.

Deficiency # 5
Created in C3
Prescribing Information

(b) (4)

Response / Assessment:

Deficiency # 6
Created in C3
Patient Information Leaflet
Response / Assessment:

(b) (4)

Deficiency # 7
Created in C3
Carton Labeling
Response / Assessment:

Unit-dose 100s (10x10)- To be consistent with the RLD's cartons, consider adding "For Institutional Use Only." statement.

Addressed- Information added to the carton in the 11/26/2021 submission.

Deficiency # 8
Created in C4
Prescribing Information

HIGHLIGHTS

i. RECENT MAJOR CHANGES
We acknowledge your comment regarding the HIGHLIGHTS, RECENT MAJOR CHANGES request. However, please revise to read the same as the RLD labeling. (b)(4)

(b)(4)

Response / Assessment:

Deficiency #9

PRESCRIBING INFORMATION, INDICATIONS AND USAGE, Revise Section 1.1 Adult Heart Failure as follows:

Created in C4

Prescribing Information

(b)(4)

Left ventricular ejection fraction (LVEF) is a variable measure, so use clinical judgment in deciding whom to treat [see Clinical Studies (14.1)].

(b)(4)

Response / Assessment:

5.5 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:

Satisfactory in the 11/26/2021 submission.

Deficiency Comments:

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:

NA

Deficiency Comments:



Angela
Payne

Digitally signed by Angela Payne
Date: 12/01/2021 06:22:13PM
GUID: 508da70600028ab611d2ba935d5074a6



Burhan
Nour

Digitally signed by Burhan Nour
Date: 12/01/2021 06:55:53PM
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	08/25/2022
ANDA Number(s)	213676
Review Number	5
Applicant Name	Laurus Labs 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	N/A
Submission Received Date	March 17, 2022
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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1 LABELING COMMENTS (C5)

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

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

The Division of Labeling has no further questions/comments at this time based on your labeling submission received March 17, 2022.

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 (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.

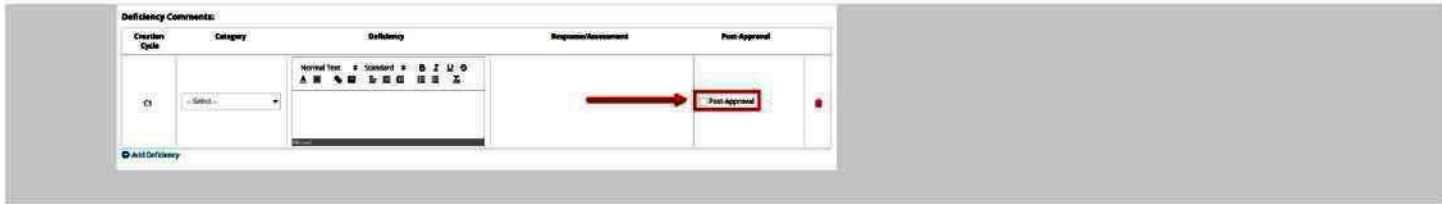
☐	☒	There is information in the Orange Book that the applicant needs to address.
☒	☐	Information in the Orange Book has expired and the applicant needs to revise labeling.

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.



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 in 30s, 60s, and 180s count bottles (b)(4)	11/7/2019	Satisfactory
Blister	Final	10s unit dose cold form and 10s pvc/aclar	11/7/2019	Satisfactory
Carton	Final	100s (10x10) unit dose	11/26/21	Satisfactory

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	Revised: 03/2022	3/17/2022	Satisfactory
Medication Guide	N/A	N/A		
Patient Information	Final	Revised: 03/2022	3/17/2022	Satisfactory
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 ? (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.

Yes	No	
		(b) (4)
☒	☐	Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? (b) (4)

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

(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

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

Proprietary Name: Entresto Tablets

Established Name: sacubitril/valsartan tablets

Description of Supplement:

SE-018- approved 02/16/2021. 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.

SE-013- approved 10/01/2019. 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 16 (CBE-30 CMC supplement): PENDING; (b)(4)

(b)(4)

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

Drug Name	Active Ingredient	Strength	Dosage Form	Route of Administration	Is Code	EC	CI
ENTRESTO	SACUBITRIL/VALSARTAN	240/160MG	TABLETS	Oral	Yes	Yes	Yes
ENTRESTO	SACUBITRIL/VALSARTAN	495MG	TABLETS	Oral	Yes	Yes	Yes
ENTRESTO	SACUBITRIL/VALSARTAN	495MG	TABLETS	Oral	Yes	Yes	Yes

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.

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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.

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	IV	12/23/2021	None
24MG;26MG, 49MG;51MG, 97MG;103MG	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	IV		None
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	12/23/2021	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
24MG;26MG, 49MG;51MG, 97MG;103MG	11135192	08/22/2033	U-3084	TREATMENT OF HEART FAILURE WITH PRESERVED EJECTION FRACTION	viii		Carve-out
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	7468390	11/27/2023					
97MG;103MG, 49MG;51MG, 24MG;26MG	7468390	11/27/2023			IV	07/08/2019	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	7468390*PED	05/27/2024					
97MG;103MG, 49MG;51MG, 24MG;26MG	7468390*PED	05/27/2024			IV	07/08/2019	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	8101659	01/15/2025					
49MG;51MG, 97MG;103MG, 24MG;26MG	8101659	01/14/2023			IV	07/08/2019	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	8101659*PED	07/15/2025					
97MG;103MG, 49MG;51MG, 24MG;26MG	8101659*PED	07/14/2023			IV	07/08/2019	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	8404744	01/14/2023					
49MG;51MG, 24MG;26MG, 97MG;103MG	8404744	01/14/2023			IV	07/08/2019	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	8404744*PED	07/14/2023					
97MG;103MG, 49MG;51MG, 24MG;26MG	8404744*PED	07/14/2023			IV	07/08/2019	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	8796331	01/14/2023	U-1723	TREATMENT OF HEART FAILURE			
49MG;51MG, 97MG;103MG, 24MG;26MG	8796331	01/14/2023	U-1723	TREATMENT OF HEART FAILURE	IV	07/08/2019	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
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	8796331*PED	07/14/2023					
97MG;103MG, 49MG;51MG, 24MG;26MG	8796331*PED	07/14/2023			IV	07/08/2019	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	8877938	05/27/2027					
97MG;103MG, 49MG;51MG, 24MG;26MG	8877938	05/27/2027			IV	07/08/2019	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	8877938*PED	11/27/2027					
97MG;103MG, 49MG;51MG, 24MG;26MG	8877938*PED	11/27/2027			IV	07/08/2019	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	9388134	11/08/2026	U-1723	TREATMENT OF HEART FAILURE			
24MG;26MG, 97MG;103MG, 49MG;51MG	9388134	11/08/2026	U-1723	TREATMENT OF HEART FAILURE	IV	07/08/2019	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	9388134*PED	05/08/2027					
97MG;103MG, 49MG;51MG, 24MG;26MG	9388134*PED	05/08/2027			IV	07/08/2019	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			
24MG;26MG, 49MG;51MG, 97MG;103MG	9517226	08/22/2033	U-3084	TREATMENT OF HEART FAILURE WITH PRESERVED EJECTION FRACTION	viii	05/03/2021	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			

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
24MG;26MG, 49MG;51MG, 97MG;103MG	9937143	08/22/2033	U-3084	TREATMENT OF HEART FAILURE WITH PRESERVED EJECTION FRACTION	viii	05/03/2021	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
97MG;103MG, 49MG;51MG, 24MG;26MG	NCE PED	01/07/2021	NEW CHEMICAL ENTITY; PEDIATRIC EXCLUSIVITY	does not intend to market prior to the expiration of the NCE exclusivity	07/08/2019	Expired
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	NPP	10/01/2022	NEW PATIENT POPULATION			
49MG;51MG, 97MG;103MG, 24MG;26MG	NPP/S-013	10/01/2022	NEW PATIENT POPULATION	does not intend to market prior to the expiration of the NCE exclusivity. S-013	11/07/2019	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	NPP PED	04/01/2023	NEW PATIENT POPULATION; PEDIATRIC EXCLUSIVITY			
97MG;103MG, 49MG;51MG, 24MG;26MG	NPP PED	04/01/2023	NEW PATIENT POPULATION; PEDIATRIC EXCLUSIVITY	does not intend to market prior to the expiration of the NCE exclusivity	11/07/2019	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	M-82	02/16/2024	LABELING REVISIONS RELATED TO CLINICAL STUDIES			

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
49MG;51MG, 97MG;103MG, 24MG;26MG	M-82	02/16/2024	LABELING REVISIONS RELATED TO CLINICAL STUDIES	will launch prior to expiry of M-82 exclusivity,	05/03/2021	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

GENERAL

Created in C4

General Comments

i. Address the new information (or new patents/exclusivities) listed in the Orange Book for the reference listed drug (RLD), NDA 207620. Additionally, ensure all patent certifications and exclusivity statements are congruent among themselves and with the proposed labeling.

ii. Address patent number(s), 11135192 and 11058667 as listed in the "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book").

Response / Assessment:

Addressed 12/23/2021.

4.4 UNITED STATES PHARMACOPEIA (USP) (C5)

The USP was searched on 08/25/2022

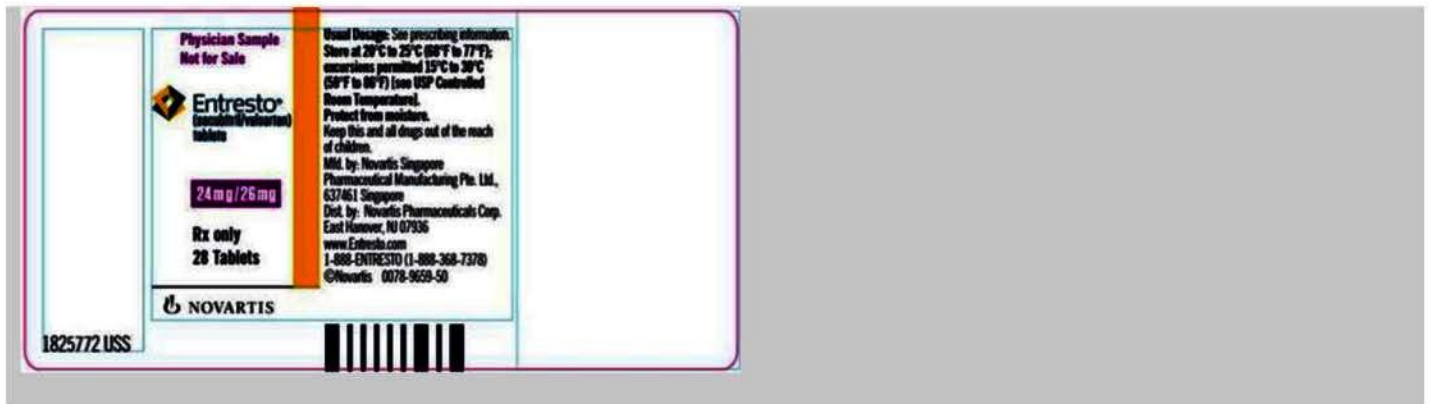
Table 6: USP				
	YES or NO	Date	Monograph Title (N/A if no monograph)	Packaging and Storage/Labeling Statements (N/A if no monograph)
Currently Official	No		N/A	N/A
Not Yet Official	No		N/A	N/A

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.
☐	☒	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: labels (Source: DARRTS; S-016, approved 2/20/2020) storage statement updated.)



NDC 0078-0777-67
Entresto
 (sacubitril/valsartan)
 tablets
 49 mg/51 mg
 Rx only
 180 Tablets
 NOVARTIS
 © 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.
 Mfg. 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)

0078-0777-67
 1826200 US

NDC 0078-0696-20
Entresto
 (sacubitril/valsartan)
 tablets
 97 mg/103 mg
 Rx only
 60 Tablets
 NOVARTIS
 © 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.
 Mfg. 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)

0078-0696-20
 1826201 US

DARRTS; ANRPT-4 submitted 8/30/2019. Note storage is not updated per S-016.

NDC 0078-0659-67
Entresto
 (sacubitril/valsartan)
 tablets
 24 mg/26 mg
 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.
 Mfg. 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 121253 US

0078-0659-67
 1826202 US

**Physician Sample
 Not for Sale**
Entresto
 (sacubitril/valsartan)
 tablets
 24 mg/26 mg
 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.
 Mfg. 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 0079-9009-50 120127 US

0078-0659-67
 1826203 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 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.
 Mfg. 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

0078-0659-20
 1826204 US


 NDC 0078-0777-67
Entresto®
 (sacubitril/valsartan)
 tablets
49mg/51mg
 Rx only
 180 Tablets


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.
 Mfg. 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


 Physician Sample
 Not for Sale
Entresto®
 (sacubitril/valsartan)
 tablets
49mg/51mg
 Rx only 28 Tablets


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.
 Mfg. 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 0078-5777-30 121138 US


 NDC 0078-0777-20
Entresto®
 (sacubitril/valsartan)
 tablets
49mg/51mg
 Rx only
 60 Tablets


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.
 Mfg. 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


 NDC 0078-0696-67
Entresto®
 (sacubitril/valsartan)
 tablets
97mg/103mg
 Rx only
 180 Tablets


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.
 Mfg. 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


 NDC 0078-0696-20
Entresto®
 (sacubitril/valsartan)
 tablets
97mg/103mg
 Rx only
 60 Tablets


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.
 Mfg. 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 121256 US

Model container/carton/blister labels (Source: DARRTS; ANRPT-3 submitted 8/30/2018). The RLD has delisted blister packs

24 mg / 26 mg

Entresto™
(Sacubitril/Valsartan) Tablets

NDC 0279-0259-35

Usual Dosage: See prescribing information.
Store at 20°C (67°F); excursions permitted to 15°C to 30°C (59°F to 86°F) (see USP controlled room temperature). Protect from moisture.

This package is for in-institution use only, as contents are NOT CHILD-RESISTANT. Do not distribute for household use. Keep the pack out of the reach of children.

Mfg. by Novartis Singapore Pharmaceutical Manufacturing Pte. Ltd.
SINGAPORE

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

www.entresto.com
1-800-441-9323 (1-800-441-9323)

1 357-690-23-2

© Novartis 13732-0259

NDC 0279-0259-35

Entresto™
(Sacubitril/Valsartan) Tablets

24 mg / 26 mg

Rx only 300 Tablets (30 x 10-Count Unit Dose)

NDC 0279-0259-35

Entresto™
(Sacubitril/Valsartan) Tablets

24 mg / 26 mg

Rx only 300 Tablets (30 x 10-Count Unit Dose)

NOVARTIS

49 mg / 51 mg

Entresto™
(Sacubitril/Valsartan) Tablets

NDC 0279-0777-35

Usual Dosage: See prescribing information.
Store at 20°C (67°F); excursions permitted to 15°C to 30°C (59°F to 86°F) (see USP controlled room temperature). Protect from moisture.

This package is for in-institution use only, as contents are NOT CHILD-RESISTANT. Do not distribute for household use. Keep the pack out of the reach of children.

Mfg. by Novartis Singapore Pharmaceutical Manufacturing Pte. Ltd.
SINGAPORE

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

www.entresto.com
1-800-441-9323 (1-800-441-9323)

1 357-777-8-001

© Novartis 13732-0777

NDC 0279-0777-35

Entresto™
(Sacubitril/Valsartan) Tablets

49 mg / 51 mg

Rx only 300 Tablets (30 x 10-Count Unit Dose)

NDC 0279-0777-35

Entresto™
(Sacubitril/Valsartan) Tablets

49 mg / 51 mg

Rx only 300 Tablets (30 x 10-Count Unit Dose)

NOVARTIS

113 mg / 132 mg

Entresto™
(Sacubitril/Valsartan) Tablets

NDC 0279-0261-35

Usual Dosage: See prescribing information.
Store at 20°C (67°F); excursions permitted to 15°C to 30°C (59°F to 86°F) (see USP controlled room temperature). Protect from moisture.

This package is for in-institution use only, as contents are NOT CHILD-RESISTANT. Do not distribute for household use. Keep the pack out of the reach of children.

Mfg. by Novartis Singapore Pharmaceutical Manufacturing Pte. Ltd.
SINGAPORE

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

www.entresto.com
1-800-441-9323 (1-800-441-9323)

1 357-690-23-2

© Novartis 13732-0261

NDC 0279-0261-35

Entresto™
(Sacubitril/Valsartan) Tablets

113 mg / 132 mg

Rx only 300 Tablets (30 x 10-Count Unit Dose)

NDC 0279-0261-35

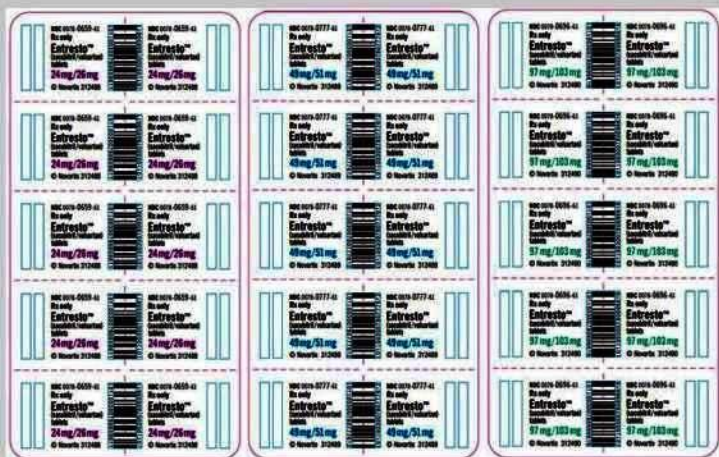
Entresto™
(Sacubitril/Valsartan) Tablets

113 mg / 132 mg

Rx only 300 Tablets (30 x 10-Count Unit Dose)

NOVARTIS

Model container/carton/blister labels (Source: DARRTS; ANRPT-1 submitted 8/30/2016). The applicant is no longer marketing blisters container/cartons.



5 ASSESSMENT OF ANDA LABELING AND LABELS (C5)

5.1 QUALITY INFORMATION (DRUG PRODUCT MOU & BIOPHARMACEUTICS) (C5)

5.1.1 DRUG PRODUCT REVIEW (C5)

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

R03, 9/22/2021

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	Dimension (mm) (Length x Width)	Imprint Code
24mg/26mg	9.11x 5.08	Violet white color, oval, biconvex film-coated tablets debossed with "S5" on one side and plain on the other side.
49mg/51mg	12.75 x 5.90	Pale yellow color, oval, biconvex film-coated tablets debossed with "S1" on one side and plain on the other side.
97mg/103mg	12.57 x 6.85	Light pink color, oval, biconvex film-coated tablets debossed with "S2" on one side and plain on the other side.

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	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

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

	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	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 crospovidone, low-substituted hydroxypropylcellulose, magnesium stearate, microcrystalline cellulose, and silicon dioxide. The film-coat inactive ingredients are hypromellose, titanium dioxide, Macrogol 4000, talc, and iron oxide red. 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. The film-coat for the 49 mg of sacubitril and 51 mg of valsartan tablet contains iron oxide yellow.
Current ANDA Labeling	11 DESCRIPTION Sacubitril and valsartan tablets are a combination of a neprilysin inhibitor and an angiotensin II receptor blocker. Sacubitril and valsartan tablets contain a complex comprised of anionic forms of sacubitril and valsartan, and sodium cations in the molar ratio of 1:1:3, respectively. Following oral administration, the complex dissociates into sacubitril (which is further metabolized to LBQ657) and valsartan. The complex is chemically described as Tri sodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbonyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate]. Its molecular formula is C₄₈H₅₅N₆O₈•3Na. Its molecular mass is 912.95 and its schematic structural formula is: 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 crospovidone, low-substituted hydroxypropylcellulose, magnesium stearate, microcrystalline cellulose, and silicon dioxide. The film-coat inactive ingredients are hypromellose, titanium dioxide, Macrogol 4000, talc, and iron oxide red. 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. The film-coat for the 49 mg of sacubitril and 51 mg of valsartan tablet contains iron oxide yellow. Current cycle 5. No changes

5.1.3 HOW SUPPLIED/STORAGE AND HANDLING (C5)

Table 8: Comparison of Model Labeling to ANDA Labeling

Model Labeling	16 HOW SUPPLIED/STORAGE AND HANDLING ENTRESTO (sacubitril/valsartan) is available as uncoated, 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 border="1" data-bbox="483 235 1003 424"> <thead> <tr> <th>Tablet</th> <th>Color</th> <th>Debossment</th> <th colspan="2">NDC # 0078-XXXX-XX</th> </tr> </thead> <tbody> <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> </tbody> </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	16 HOW SUPPLIED/STORAGE AND HANDLING Sacubitril and valsartan tablets are available as described below: Sacubitril and valsartan tablets 24/26 mg, (sacubitril 24 mg and valsartan 26 mg) are violet white color, oval shaped, biconvex film-coated tablets debossed with "S5" on one side and plain on the other side. Bottles of 30 NDC 42385-930-30 Bottles of 60 NDC 42385-930-60 Bottles of 180 NDC 42385-930-18 Carton with 100 (10 x 10) Unit-Dose Tablets containing cold form with desiccant blisters NDC 42385-930-68 Carton with 100 (10 x 10) Unit-Dose Tablets containing PVC/ACLAR blisters NDC 42385-930-72 Sacubitril and valsartan tablets 49/51 mg, (sacubitril 49 mg and valsartan 51 mg) are pale yellow color, oval shaped, biconvex film-coated tablets debossed with "S1" on one side and plain on the other side. Bottles of 30 NDC 42385-931-30 Bottles of 60 NDC 42385-931-60 Bottles of 180 NDC 42385-931-18 Carton with 100 (10 x 10) Unit-Dose Tablets containing cold form with desiccant blisters NDC 42385-931-68 Carton with 100 (10 x 10) Unit-Dose Tablets containing PVC/ACLAR blisters NDC 42385-931-72 Sacubitril and valsartan tablets 97/103 mg, (sacubitril 97 mg and valsartan 103 mg) are light pink color, oval shaped, biconvex film-coated tablets debossed with "S2" on one side and plain on the other side. Bottles of 30 NDC 42385-932-30 Bottles of 60 NDC 42385-932-60 Bottles of 180 NDC 42385-932-18 Carton with 100 (10 x 10) Unit-Dose Tablets containing cold form with desiccant blisters NDC 42385-932-68 Carton with 100 (10 x 10) Unit-Dose Tablets containing PVC/ACLAR blisters NDC 42385-932-72 Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature]. Protect from moisture.																									
Current ANDA Labeling	16 HOW SUPPLIED/STORAGE AND HANDLING Sacubitril and valsartan tablets are available as described below: Sacubitril and valsartan tablets 24/26 mg, (sacubitril 24 mg and valsartan 26 mg) are violet white color, oval shaped, biconvex film-coated tablets debossed with "S5" on one side and plain on the other side. Bottles of 30 NDC 42385-930-30 Bottles of 60 NDC 42385-930-60 Bottles of 180 NDC 42385-930-18 Carton with 100 (10 x 10) Unit-Dose Tablets containing cold form with desiccant blisters NDC 42385-930-68 Carton with 100 (10 x 10) Unit-Dose Tablets containing PVC/ACLAR blisters NDC 42385-930-72																									

Table 8: Comparison of Model Labeling to ANDA Labeling

	Sacubitril and valsartan tablets 49/51 mg, (sacubitril 49 mg and valsartan 51 mg) are pale yellow color, oval shaped, biconvex film-coated tablets debossed with “S1” on one side and plain on the other side. Bottles of 30 NDC 42385-931-30 Bottles of 60 NDC 42385-931-60 Bottles of 180 NDC 42385-931-18 Carton with 100 (10 x 10) Unit-Dose Tablets containing cold form with desiccant blisters NDC 42385-931-68 Carton with 100 (10 x 10) Unit-Dose Tablets containing PVC/ACLAR blisters NDC 42385-931-72 Sacubitril and valsartan tablets 97/103 mg, (sacubitril 97 mg and valsartan 103 mg) are light pink color, oval shaped, biconvex film-coated tablets debossed with “S2” on one side and plain on the other side. Bottles of 30 NDC 42385-932-30 Bottles of 60 NDC 42385-932-60 Bottles of 180 NDC 42385-932-18 Carton with 100 (10 x 10) Unit-Dose Tablets containing cold form with desiccant blisters NDC 42385-932-68 Carton with 100 (10 x 10) Unit-Dose Tablets containing PVC/ACLAR blisters NDC 42385-932-72 Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature]. Protect from moisture. current cycle 5, no changes.

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	(b)(4)
Current ANDA Labeling	
Name and Address on ANDA Prescribing Information	(b)(4)

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

Manufactured by	Manufactured for	Distributed by	Distributed for
(b)(4)	Manufactured for: Laurus Generics Inc. 400 Connell Drive Suite 5200 Berkeley Heights, NJ 07922 Revised: 11/2021		

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.	
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)].	
☐	☒	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:			
Container labels found satisfactory during previous cycles in the submissions dated as follows:			
	Final or Draft or NA	Packaging Sizes	Submission Received Date
Container	Final	24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg in 30s, 60s, and 180s count bottles (b)(4)	11/7/2019
Blister	Final	10s unit dose cold form and 10s pyc/aclar.	11/7/2019
Carton	Final	100s (10x10) unit dose	11/26/21
Deficiency Comments:			

5.2.1 UNIT-DOSE BLISTERS(C5)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Each blister contains only one dosage unit (e.g. one tablet, one capsule).
☐	☒	Established/proprietary name, strength, bar code, and manufacturer/distributor/packer appear accurately on each blister cell.
Reviewer Comments: Satisfactory in the previous cycle 2.		
Deficiency Comments:		

5.3 CARTON (OUTER OR SECONDARY PACKAGING) LABELING (C5)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	The answers to the Container Label questions are the same for the Carton Labeling. Please enter Reviewer/Deficiency Comments if you select Deficiency.
Reviewer Comments: U/D carton labels are satisfactory in the 11/26/2021 submission.		
Deficiency Comments:		

5.4 PRESCRIBING INFORMATION (C5)

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.

Deficiency	No Deficiency	
☐	☒	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 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)

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)

Response / Assessment:

5.5 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: Satisfactory in the 3/23/2022 submission (b)(4)		
Deficiency Comments:		

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: NA	
Deficiency Comments:	



Angela
Payne

Digitally signed by Angela Payne
Date: 9/05/2022 06:03:51PM
GUID: 508da70600028ab611d2ba935d5074a6



Burhan
Nour

Digitally signed by Burhan Nour
Date: 9/13/2022 07:53:20PM
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	12/14/2022
ANDA Number(s)	213676
Review Number	6
Applicant Name	Laurus Labs 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	N/A
Submission Received Date	September 23, 2022
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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1 LABELING COMMENTS (C6)

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

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

The Division of Labeling has no further questions/comments at this time based on your labeling submission received September 23, 2022.

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 (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.



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	24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg in 30s, 60s, and 180s count bottles (b)(4)	11/7/2019	Satisfactory
Blister	Final	10s unit dose cold form and 10s pvc/aclar	11/7/2019	Satisfactory
Carton	Final	100s (10x10) unit dose	11/26/21	Satisfactory

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	Revised: 09/2022	09/23/2022	Satisfactory
Medication Guide	N/A	N/A		
Patient Information	Final	Revised: 09/2022	09/23/2022	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 ? (b) (4)

Yes	No																					
		Add File - DLR Drug Facts File Folder Add a new document to help with the review process by clicking the image below. You will be asked a series of questions to help classify the document(s) so that they are added to the proper place. Please note that this is not to replace the Platform in any way if something already exists on the Platform - Please link it to the review on the Platform. <table border="1" data-bbox="414 283 1112 911"> <tr> <td data-bbox="414 283 592 315">Title</td> <td data-bbox="592 283 1112 315">Entresto (sacubitril and valsartan), NDA 207620/S-018, Citizen Petition- languag...</td> </tr> <tr> <td data-bbox="414 315 592 346">Date:</td> <td data-bbox="592 315 1112 346">11/16/2022</td> </tr> <tr> <td data-bbox="414 346 592 388">Is this a Review?</td> <td data-bbox="592 346 1112 388">☐</td> </tr> <tr> <td data-bbox="414 388 592 472">What Type of File?</td> <td data-bbox="592 388 1112 472">E-mails</td> </tr> <tr> <td data-bbox="414 472 592 556">Attachments</td> <td data-bbox="592 472 1112 556">FW Entresto CP disclaimer language (v4) for inadequate labeling .msg</td> </tr> <tr> <td data-bbox="414 556 592 598">Hyperlink to Review</td> <td data-bbox="592 556 1112 598"> No hyperlink inserted</td> </tr> <tr> <td data-bbox="414 598 592 724">Active Ingredient</td> <td data-bbox="592 598 1112 724"> ☒ sacubitril and valsartan ☒ Sacubitril and Valsartan </td> </tr> <tr> <td data-bbox="414 724 592 756">Dosage Forms:</td> <td data-bbox="592 724 1112 756">Tablets</td> </tr> <tr> <td data-bbox="414 756 592 787">Manufacturer:</td> <td data-bbox="592 756 1112 787">Novartis Consumer Health, Inc.</td> </tr> <tr> <td data-bbox="414 787 592 911">Brief Description</td> <td data-bbox="592 787 1112 911"> Per Policy, include the following paragraphs (Version 4) in "inadequate" labeling review comments. As of 11/16/2022 version (V4) supersedes the previous versions (V.1, V.2, and V.3). See guidance below: </td> </tr> </table>	Title	Entresto (sacubitril and valsartan), NDA 207620/S-018, Citizen Petition- languag...	Date:	11/16/2022	Is this a Review?	☐	What Type of File?	E-mails	Attachments	FW Entresto CP disclaimer language (v4) for inadequate labeling .msg	Hyperlink to Review	No hyperlink inserted	Active Ingredient	☒ sacubitril and valsartan ☒ Sacubitril and Valsartan	Dosage Forms:	Tablets	Manufacturer:	Novartis Consumer Health, Inc.	Brief Description	Per Policy, include the following paragraphs (Version 4) in "inadequate" labeling review comments. As of 11/16/2022 version (V4) supersedes the previous versions (V.1, V.2, and V.3). See guidance below:
Title	Entresto (sacubitril and valsartan), NDA 207620/S-018, Citizen Petition- languag...																					
Date:	11/16/2022																					
Is this a Review?	☐																					
What Type of File?	E-mails																					
Attachments	FW Entresto CP disclaimer language (v4) for inadequate labeling .msg																					
Hyperlink to Review	No hyperlink inserted																					
Active Ingredient	☒ sacubitril and valsartan ☒ Sacubitril and Valsartan																					
Dosage Forms:	Tablets																					
Manufacturer:	Novartis Consumer Health, Inc.																					
Brief Description	Per Policy, include the following paragraphs (Version 4) in "inadequate" labeling review comments. As of 11/16/2022 version (V4) supersedes the previous versions (V.1, V.2, and V.3). See guidance below:																					

Yes	No	
		See guidance below: GENERAL COMMENTS: a. 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 regulatory and patent exclusivities: 1) Entresto’s 3-year exclusivity expiring on February 16, 2024, and denoted in FDA’s Orange Book with the exclusivity code “M-82: Labeling Revisions Related to Clinical Studies;” 2) 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 (3) 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). 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, Entresto’s unexpired 3-year exclusivity, and Orange Book-listed patents. b. 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. *****

Yes	No	
		✓ VERSION 4 (11/16/2022) provides for revised CP language, from OGDG for DrugFacts file folder, for deficient labeling reviews. This new entry 11/16/2022 supersedes the previously posted entries dated 3/22/2022, 7/6/2022, and 8/29/2022. Guidance to the labeling assessor for including OGDG CP disclaimer language: Copy and paste OGDG's CP disclaimer language as a "General Comment (s)" in the labeling review. This general disclaimer language is required irrespective of how an applicant filed or addressed the OB patents and/or exclusivities and is required when the ANDA review is deficient (DRLs/IRs/CRLs) for labeling. (Do not include the general comment when the review is adequate). The disclaimer acknowledges the citizen petition submitted by the brand owner and permits the agency to make additional labeling request based on the Agency current thinking surrounding the CP, if needed going forward prior to full approval. ● (b) (4)

Yes	No																										
		(b)(4)																									
		12/14/2022- As of this cycle (6) this review is adequate, (b)(4)	(b)(4)																								
☒	☐	Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? PAL20221209 <table border="1" data-bbox="300 1092 1023 1239"> <thead> <tr> <th>IP</th> <th>PA#</th> <th>Applicant</th> <th>Product Name</th> <th>Approval Date</th> <th>Approval Status</th> </tr> </thead> <tbody> <tr> <td>IP</td> <td>PA-2022-1209</td> <td>Entresto</td> <td>Entresto Tablets</td> <td>02/16/2021</td> <td>Approved</td> </tr> <tr> <td>IP</td> <td>PA-2022-1209</td> <td>Entresto</td> <td>Entresto Tablets</td> <td>02/16/2021</td> <td>Approved</td> </tr> <tr> <td>IP</td> <td>PA-2022-1209</td> <td>Entresto</td> <td>Entresto Tablets</td> <td>02/16/2021</td> <td>Approved</td> </tr> </tbody> </table>		IP	PA#	Applicant	Product Name	Approval Date	Approval Status	IP	PA-2022-1209	Entresto	Entresto Tablets	02/16/2021	Approved	IP	PA-2022-1209	Entresto	Entresto Tablets	02/16/2021	Approved	IP	PA-2022-1209	Entresto	Entresto Tablets	02/16/2021	Approved
IP	PA#	Applicant	Product Name	Approval Date	Approval Status																						
IP	PA-2022-1209	Entresto	Entresto Tablets	02/16/2021	Approved																						
IP	PA-2022-1209	Entresto	Entresto Tablets	02/16/2021	Approved																						
IP	PA-2022-1209	Entresto	Entresto Tablets	02/16/2021	Approved																						

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 <i>(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.)</i> NDA#/Supplement# (S-000 if original): NDA207620 / S-018 Supplement Approval Date: 02/16/2021 Proprietary Name: Entresto Tablets Established Name: sacubitril/valsartan tablets Description of Supplement: SE-018- approved 02/16/2021. This Prior Approval supplemental new drug application provides for updates to the United States Prescribing Information (USPI) and the Patient Package Insert (PPI) related

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

to the PARAGON-HF trial, including substantive revisions to Indications and Usage and Clinical Studies; additional revisions were made throughout labeling.

SE-013- approved 10/01/2019. 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 16 (CBE-30 CMC supplement): PENDING; (b)(4)

(b)(4)

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

Drug Name	Active Ingredient	Strength	Dosage Form	Marketing Status	Date
Entresto	valsartan/hydrochlorothiazide	40mg/12.5mg	Tablet	Approved	10/01/2019
Entresto	valsartan/hydrochlorothiazide	80mg/12.5mg	Tablet	Approved	10/01/2019
Entresto	valsartan/hydrochlorothiazide	160mg/12.5mg	Tablet	Approved	10/01/2019

Link: https://analytics.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 (C6)

The [Orange Book](#) was searched on 12/14/2022

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	IV	12/23/2021	None
24MG;26MG, 49MG;51MG, 97MG;103MG	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	IV		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
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	IV	09/23/2022	None
24MG;26MG, 49MG;51MG, 97MG;103MG	11135192	08/22/2033	U-3084	TREATMENT OF HEART FAILURE WITH PRESERVED EJECTION FRACTION	IV	09/23/2022	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	7468390	11/27/2023					
97MG;103MG, 49MG;51MG, 24MG;26MG	7468390	11/27/2023			IV	07/08/2019	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	7468390*PED	05/27/2024					
97MG;103MG, 49MG;51MG, 24MG;26MG	7468390*PED	05/27/2024			IV	07/08/2019	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	8101659	01/15/2025					
49MG;51MG, 97MG;103MG, 24MG;26MG	8101659	01/14/2023			IV	07/08/2019	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	8101659*PED	07/15/2025					
97MG;103MG, 49MG;51MG, 24MG;26MG	8101659*PED	07/14/2023			IV	07/08/2019	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	8404744	01/14/2023					
49MG;51MG, 24MG;26MG, 97MG;103MG	8404744	01/14/2023			IV	07/08/2019	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	8404744*PED	07/14/2023					
97MG;103MG, 49MG;51MG, 24MG;26MG	8404744*PED	07/14/2023			IV	07/08/2019	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
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	8796331	01/14/2023	U-1723	TREATMENT OF HEART FAILURE			
49MG;51MG, 97MG;103MG, 24MG;26MG	8796331	01/14/2023	U-1723	TREATMENT OF HEART FAILURE	IV	07/08/2019	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	8796331*PED	07/14/2023					
97MG;103MG, 49MG;51MG, 24MG;26MG	8796331*PED	07/14/2023			IV	07/08/2019	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	8877938	05/27/2027					
97MG;103MG, 49MG;51MG, 24MG;26MG	8877938	05/27/2027			IV	07/08/2019	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	8877938*PED	11/27/2027					
97MG;103MG, 49MG;51MG, 24MG;26MG	8877938*PED	11/27/2027			IV	07/08/2019	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	9388134	11/08/2026	U-1723	TREATMENT OF HEART FAILURE			
24MG;26MG, 97MG;103MG, 49MG;51MG	9388134	11/08/2026	U-1723	TREATMENT OF HEART FAILURE	IV	07/08/2019	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	9388134*PED	05/08/2027					
97MG;103MG, 49MG;51MG, 24MG;26MG	9388134*PED	05/08/2027			IV	07/08/2019	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			
24MG;26MG, 49MG;51MG, 97MG;103MG	9517226	08/22/2033	U-3084	TREATMENT OF HEART FAILURE WITH PRESERVED EJECTION FRACTION	IV	09/23/2022	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
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			
24MG;26MG, 49MG;51MG, 97MG;103MG	9937143	08/22/2033	U-3084	TREATMENT OF HEART FAILURE WITH PRESERVED EJECTION FRACTION	IV	09/23/2022	None

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
97MG;103MG, 49MG;51MG, 24MG;26MG	NCE PED	01/07/2021	NEW CHEMICAL ENTITY; PEDIATRIC EXCLUSIVITY	does not intend to market prior to the expiration of the NCE exclusivity	07/08/2019	Expired
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	NPP	10/01/2022	NEW PATIENT POPULATION			Expired
49MG;51MG, 97MG;103MG, 24MG;26MG	NPP/S-013	10/01/2022	NEW PATIENT POPULATION			Expired
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	NPP PED	04/01/2023	NEW PATIENT POPULATION; PEDIATRIC EXCLUSIVITY			
97MG;103MG, 49MG;51MG, 24MG;26MG	NPP PED	04/01/2023	NEW PATIENT POPULATION; PEDIATRIC EXCLUSIVITY	Seeks approval after expiration	09/23/2022	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	M-82	02/16/2024	LABELING REVISIONS RELATED TO CLINICAL STUDIES			

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
49MG;51MG, 97MG;103MG, 24MG;26MG	M-82	02/16/2024	LABELING REVISIONS RELATED TO CLINICAL STUDIES	Seeks approval after expiration.	09/23/2022	None

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:

4.4 UNITED STATES PHARMACOPEIA (USP) (C6)

The USP was searched on 12/14/2022

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.
☐	☒	ASSAY: Drug product meets USP acceptance criteria for assay.

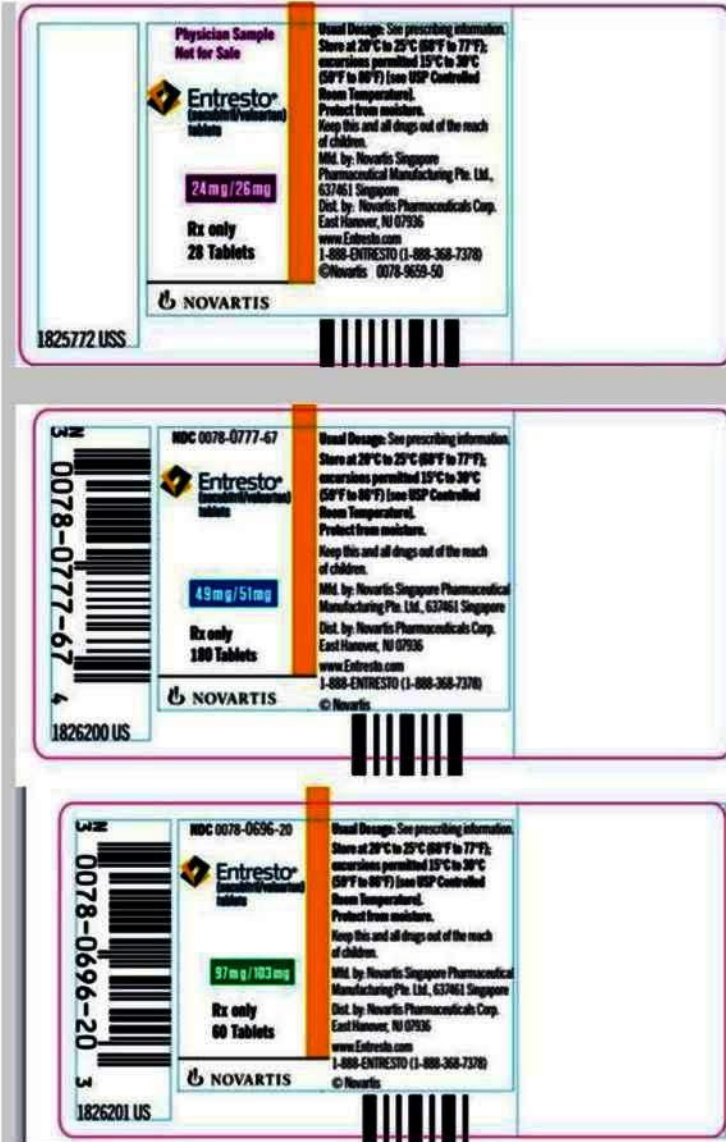
Reviewer Comments:

N/A

Deficiency Comments:

4.5 MODEL CONTAINER LABELS (C6)

Model container/carton/blister labels (Source: labels (Source: DARRTS; S-016, approved 2/20/2020) storage statement updated.)



DARRTS; ANRPT-4 submitted 8/30/2019. Note storage is not updated per S-016.


NDC 0078-0659-67

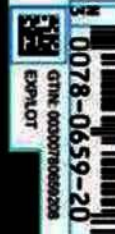
Entresto®
 (sacubitril/valsartan)
 tablets
24 mg/26 mg
 Rx only
 180 Tablets


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.
 Mfg. 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 121253 US

**Physician Sample
 Not for Sale**

Entresto®
 (sacubitril/valsartan)
 tablets
24 mg/26 mg
 Rx only 28 Tablets


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.
 Mfg. 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 0078-9009-50 12112 US


NDC 0078-0659-20

Entresto®
 (sacubitril/valsartan)
 tablets
24 mg/26 mg
 Rx only
 60 Tablets


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.
 Mfg. 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


NDC 0078-0777-67

Entresto®
 (sacubitril/valsartan)
 tablets
49 mg/51 mg
 Rx only
 180 Tablets


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.
 Mfg. 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

**Physician Sample
 Not for Sale**

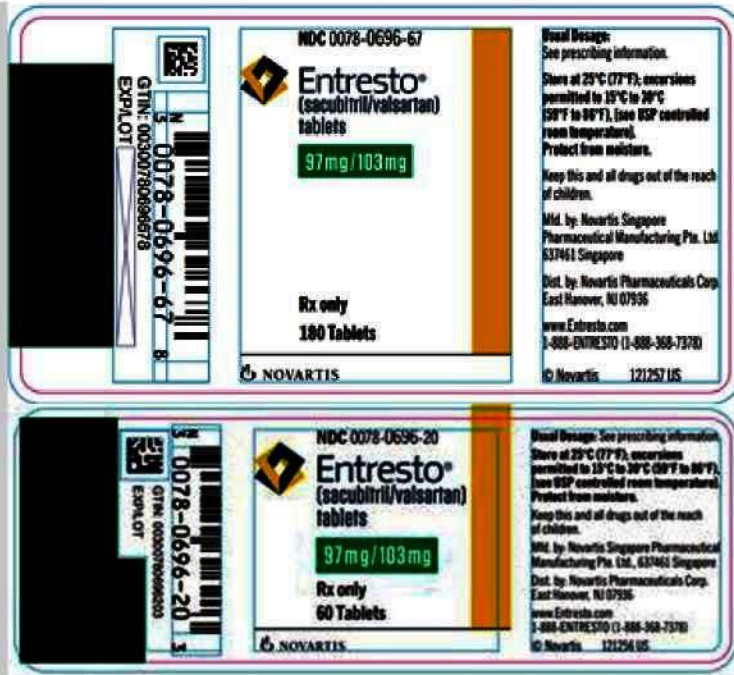
Entresto®
 (sacubitril/valsartan)
 tablets
49 mg/51 mg
 Rx only 28 Tablets


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.
 Mfg. 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 0078-5777-50 121138 US


NDC 0078-0777-20

Entresto®
 (sacubitril/valsartan)
 tablets
49 mg/51 mg
 Rx only
 60 Tablets


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.
 Mfg. 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



Model container/carton/blister labels (Source: DARRTS; ANRPT-3 submitted 8/30/2018). The RLD has delisted blister packs

24 mg / 26 mg
Entresto™
(Sacubitril/Valsartan) Tablets

Keep at 20°C (68°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP controlled room temperature]. Protect from moisture.

This package is for in-institution use only, as contents are NOT CHILD-RESISTANT. Do not distribute for household use. Keep the end of all strips out of the reach of children.

Mfg. by Novartis Singapore Pharmaceutical Manufacturing Pte. Ltd. 627612 Singapore
Dist. by Novartis Pharmaceuticals Corp. East Hanover, NJ 07930
www.entresto.com
1-800-441-9323 (1-800-441-9323)

1 357-690-23-2

© Novartis 13732-0251

NDC 0279-0259-35

Rx only 300 Tablets (30 x 10-Count Unit Dose)

Entresto™
(Sacubitril/Valsartan) Tablets
24 mg / 26 mg

NOVARTIS

49 mg / 51 mg
Entresto™
(Sacubitril/Valsartan) Tablets

Keep at 20°C (68°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP controlled room temperature]. Protect from moisture.

This package is for in-institution use only, as contents are NOT CHILD-RESISTANT. Do not distribute for household use. Keep the end of all strips out of the reach of children.

Mfg. by Novartis Singapore Pharmaceutical Manufacturing Pte. Ltd. 627612 Singapore
Dist. by Novartis Pharmaceuticals Corp. East Hanover, NJ 07930
www.entresto.com
1-800-441-9323 (1-800-441-9323)

1 357-777-84-00

© Novartis 13732-0261

NDC 0279-0277-35

Rx only 300 Tablets (30 x 10-Count Unit Dose)

Entresto™
(Sacubitril/Valsartan) Tablets
49 mg / 51 mg

NOVARTIS

17 mg / 33 mg
Entresto™
(Sacubitril/Valsartan) Tablets

Keep at 20°C (68°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP controlled room temperature]. Protect from moisture.

This package is for in-institution use only, as contents are NOT CHILD-RESISTANT. Do not distribute for household use. Keep the end of all strips out of the reach of children.

Mfg. by Novartis Singapore Pharmaceutical Manufacturing Pte. Ltd. 627612 Singapore
Dist. by Novartis Pharmaceuticals Corp. East Hanover, NJ 07930
www.entresto.com
1-800-441-9323 (1-800-441-9323)

1 357-690-23-2

© Novartis 13732-0241

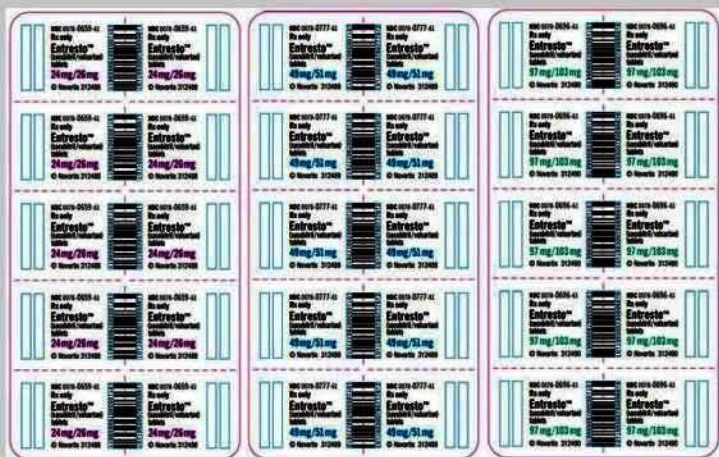
NDC 0279-0249-35

Rx only 300 Tablets (30 x 10-Count Unit Dose)

Entresto™
(Sacubitril/Valsartan) Tablets
17 mg / 33 mg

NOVARTIS

Model container/carton/blister labels (Source: DARRTS; ANRPT-1 submitted 8/30/2016). The applicant is no longer marketing blisters container/cartons.



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

R03. 9/22/2021

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	Dimension (mm) (Length x Width)	Imprint Code
24mg/26mg	9.11 x 5.08	Violet white color, oval, biconvex film-coated tablets debossed with "S5" on one side and plain on the other side.
49mg/51mg	12.75 x 5.90	Pale yellow color, oval, biconvex film-coated tablets debossed with "S1" on one side and plain on the other side.
97mg/103mg	12.57 x 6.85	Light pink color, oval, biconvex film-coated tablets debossed with "S2" on one side and plain on the other side.

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 (C6)

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

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

	ingredients are microcrystalline cellulose, low-substituted hydroxypropyl cellulose, 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	11 DESCRIPTION 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 crospovidone, low-substituted hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, and silicon dioxide. The film-coat inactive ingredients are hypromellose, titanium dioxide, Macrogol 4000, talc, and iron oxide red. 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. The film-coat for the 49 mg of sacubitril and 51 mg of valsartan tablet contains iron oxide yellow.
Current ANDA Labeling	11 DESCRIPTION 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 crospovidone, low-substituted hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, and silicon dioxide. The film-coat inactive ingredients are hypromellose, titanium dioxide, Macrogol 4000, talc, and iron oxide red. 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. The film-coat for the 49 mg of sacubitril and 51 mg of valsartan tablet contains iron oxide yellow. Labeling Assessment- current cycle (6), no changes.

5.1.3 HOW SUPPLIED/STORAGE AND HANDLING (C6)

Table 8: Comparison of Model Labeling to ANDA Labeling

Model Labeling	16 HOW SUPPLIED/STORAGE AND HANDLING 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 border="1" data-bbox="483 1566 1000 1755"> <thead> <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> </thead> <tbody> <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> </tbody> </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	16 HOW SUPPLIED/STORAGE AND HANDLING Sacubitril and valsartan tablets are available as described below:																									

Table 8: Comparison of Model Labeling to ANDA Labeling

	Sacubitril and valsartan tablets 24/26 mg, (sacubitril 24 mg and valsartan 26 mg) are violet white color, oval shaped, biconvex film-coated tablets debossed with “S5” on one side and plain on the other side. Bottles of 30 NDC 42385-930-30 Bottles of 60 NDC 42385-930-60 Bottles of 180 NDC 42385-930-18 Carton with 100 (10 x 10) Unit-Dose Tablets containing cold form with desiccant blisters NDC 42385-930-68 Carton with 100 (10 x 10) Unit-Dose Tablets containing PVC/ACLAR blisters NDC 42385-930-72 Sacubitril and valsartan tablets 49/51 mg, (sacubitril 49 mg and valsartan 51 mg) are pale yellow color, oval shaped, biconvex film-coated tablets debossed with “S1” on one side and plain on the other side. Bottles of 30 NDC 42385-931-30 Bottles of 60 NDC 42385-931-60 Bottles of 180 NDC 42385-931-18 Carton with 100 (10 x 10) Unit-Dose Tablets containing cold form with desiccant blisters NDC 42385-931-68 Carton with 100 (10 x 10) Unit-Dose Tablets containing PVC/ACLAR blisters NDC 42385-931-72 Sacubitril and valsartan tablets 97/103 mg, (sacubitril 97 mg and valsartan 103 mg) are light pink color, oval shaped, biconvex film-coated tablets debossed with “S2” on one side and plain on the other side. Bottles of 30 NDC 42385-932-30 Bottles of 60 NDC 42385-932-60 Bottles of 180 NDC 42385-932-18 Carton with 100 (10 x 10) Unit-Dose Tablets containing cold form with desiccant blisters NDC 42385-932-68 Carton with 100 (10 x 10) Unit-Dose Tablets containing PVC/ACLAR blisters NDC 42385-932-72 Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature]. Protect from moisture.
Current ANDA Labeling	16 HOW SUPPLIED/STORAGE AND HANDLING Sacubitril and valsartan tablets are available as described below: Sacubitril and valsartan tablets 24/26 mg, (sacubitril 24 mg and valsartan 26 mg) are violet white color, oval shaped, biconvex film-coated tablets debossed with “S5” on one side and plain on the other side. Bottles of 30 NDC 42385-930-30 Bottles of 60 NDC 42385-930-60 Bottles of 180 NDC 42385-930-18 Carton with 100 (10 x 10) Unit-Dose Tablets containing cold form with desiccant blisters NDC 42385-930-68 Carton with 100 (10 x 10) Unit-Dose Tablets containing PVC/ACLAR blisters NDC 42385-930-72 Sacubitril and valsartan tablets 49/51 mg, (sacubitril 49 mg and valsartan 51 mg) are pale yellow color, oval shaped, biconvex film-coated tablets debossed with “S1” on one side and plain on the other side. Bottles of 30 NDC 42385-931-30 Bottles of 60 NDC 42385-931-60 Bottles of 180 NDC 42385-931-18 Carton with 100 (10 x 10) Unit-Dose Tablets containing cold form with desiccant blisters NDC 42385-931-68 Carton with 100 (10 x 10) Unit-Dose Tablets containing PVC/ACLAR blisters NDC 42385-931-72

Table 8: Comparison of Model Labeling to ANDA Labeling

	Sacubitril and valsartan tablets 97/103 mg, (sacubitril 97 mg and valsartan 103 mg) are light pink color, oval shaped, biconvex film-coated tablets debossed with “S2” on one side and plain on the other side. Bottles of 30 NDC 42385-932-30 Bottles of 60 NDC 42385-932-60 Bottles of 180 NDC 42385-932-18 Carton with 100 (10 x 10) Unit-Dose Tablets containing cold form with desiccant blisters NDC 42385-932-68 Carton with 100 (10 x 10) Unit-Dose Tablets containing PVC/ACLAR blisters NDC 42385-932-72 Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature]. Protect from moisture. Labeling Assessment- Current cycle (6), no changes.

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	(b)(4)
Current ANDA Labeling	
Name and Address on ANDA Prescribing Information	(b)(4)

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

Manufactured by	Manufactured for	Distributed by	Distributed for
(b)(4)	Manufactured for: Laurus Generics Inc. 400 Connell Drive Suite 5200 Berkeley Heights, NJ 07922 Revised: 11/2021		

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.

Deficiency	No Deficiency																	
☐	☒	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)].																
☐	☒	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:																		
Container labels were satisfactory during previous cycles on submission dates indicated as follows:																		
<table border="1"> <thead> <tr> <th></th> <th>Final or Draft or NA</th> <th>Packaging Sizes</th> <th>Submission Received Date</th> </tr> </thead> <tbody> <tr> <td>Container</td> <td>Final</td> <td>24 mg/26 mg, 48 mg/51 mg and 97 mg/103 mg in 30s, 60s, and 180s count bottles (b)(4)</td> <td>11/7/2019</td> </tr> <tr> <td>Blister</td> <td>Final</td> <td>10s unit dose cold form and 10s pvc/aclar</td> <td>11/7/2019</td> </tr> <tr> <td>Carton</td> <td>Final</td> <td>100s (10x10) unit dose</td> <td>11/26/21</td> </tr> </tbody> </table>				Final or Draft or NA	Packaging Sizes	Submission Received Date	Container	Final	24 mg/26 mg, 48 mg/51 mg and 97 mg/103 mg in 30s, 60s, and 180s count bottles (b)(4)	11/7/2019	Blister	Final	10s unit dose cold form and 10s pvc/aclar	11/7/2019	Carton	Final	100s (10x10) unit dose	11/26/21
	Final or Draft or NA	Packaging Sizes	Submission Received Date															
Container	Final	24 mg/26 mg, 48 mg/51 mg and 97 mg/103 mg in 30s, 60s, and 180s count bottles (b)(4)	11/7/2019															
Blister	Final	10s unit dose cold form and 10s pvc/aclar	11/7/2019															
Carton	Final	100s (10x10) unit dose	11/26/21															
Deficiency Comments:																		

5.2.1 UNIT-DOSE BLISTERS(C6)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Each blister contains only one dosage unit (e.g. one tablet, one capsule).

Deficiency	No Deficiency	
☐	☒	Established/proprietary name, strength, bar code, and manufacturer/distributor/packer appear accurately on each blister cell.
Reviewer Comments: Satisfactory in the previous cycle (2).		
Deficiency Comments:		

5.3 CARTON (OUTER OR SECONDARY PACKAGING) LABELING (C6)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	The answers to the Container Label questions are the same for the Carton Labeling. Please enter Reviewer/Deficiency Comments if you select Deficiency.
Reviewer Comments: U/D carton labels are satisfactory in the 11/26/2021 submission.		
Deficiency Comments:		

5.4 PRESCRIBING INFORMATION (C6)

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.

Deficiency	No Deficiency	
☐	☒	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 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)		
12/14/2022 Assessment: Prescribing information and Patient leaflet submitted 9/23/2022 are adequate.		
Deficiency Comments:		

5.5 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: Satisfactory in the 9/23/2022 submission.		
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)	

Reviewer Comments:

NA

Deficiency Comments:



Angela
Payne

Digitally signed by Angela Payne
Date: 12/14/2022 01:28:42PM
GUID: 508da70600028ab611d2ba935d5074a6



Burhan
Nour

Digitally signed by Burhan Nour
Date: 12/14/2022 03:03:26PM
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	12/14/2022, 05/17/2024
ANDA Number(s)	213676
Review Number	6 Addendum (Updated labeling to align with the RLD/S-025.)
Applicant Name	Laurus Labs 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	N/A
Submission Received Date	September 23, 2022, May 15, 2024
Primary Labeling Reviewer	Angela Payne, RPh
Secondary Labeling Reviewer	Burhan Nour
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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1 LABELING COMMENTS (C6 ADDENDUM)

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

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

The Division of Labeling has no further questions/comments at this time based on your labeling submission received September 23, 2022, and **May 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 (C6 ADDENDUM)

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

2 INSTRUCTIONS FOR ASSESSMENT (C6 ADDENDUM)

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.



3 OVERALL ASSESSMENT OF MATERIALS REVIEWED (C6 ADDENDUM)

Table 1: Review Summary of Container Label and Carton Labeling

	Final or Draft or NA	Packaging Sizes	Submission Received Date	Recommendation
Container	Final	A) 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg in bottles of 30s, 60s, and 180s count (b)(4)	11/07/2019	Satisfactory
Blister	Final	All strengths: B) 10s unit dose (cold form) C) 10s unit dose (pvc/aclar)	07/08/2019	Satisfactory
Carton	Final	All strengths: B) 100s (10x10) unit dose of (cold form) C) 100s (10x10) unit dose of (pvc/aclar)	11/26/21	Satisfactory

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	Revised: 05/2024	05/15/2024	Satisfactory
Medication Guide	N/A	N/A		
Patient Information	Final	Revised: 05/2024	05/15/2024	Satisfactory
Instructions for Use	N/A	N/A		
SPL Data Elements				

4 LABELING REVIEW INFORMATION(C6 ADDENDUM)

4.1 REGULATORY INFORMATION (C6 ADDENDUM)

Yes	No	
☒	☐	Are there any applicable issues in DLR's SharePoint Drug Facts ? C6-Notable updates: (b) (4)

Yes	No	
		3) Policy CP disclaimer language (updated to version 5) issued to DLR on 5/9/2024 to be used for inadequate reviews.
☒	☐	Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? (b) (4)

4.2 MODEL PRESCRIBING INFORMATION (C6 ADDENDUM)

**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® Tablets

Established Name: Sacubitril/Valsartan Tablets

Description of Supplement:

This NDA and sNDA provide for the use of Entresto (sacubitril/valsartan) tablets (b)(4) 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.

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

Drug Name	Active Ingredient	Strength	Formulation	Proprietary Name	OTC Code	PL	SL
AMPHI	AMPHI	50MG/50ML	SOLUTION	AMPHI		Yes	Yes
AMPHI	AMPHI	50MG/50ML	SOLUTION	AMPHI		Yes	Yes
AMPHI	AMPHI	50MG/50ML	SOLUTION	AMPHI		Yes	Yes

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

Reviewer Assessment:

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

Reviewer Comments:

(b) (4)

(b) (4)

Deficiency Comments:

4.3 PATENTS AND EXCLUSIVITIES (C6 ADDENDUM)

The Orange Book was searched on 05/17/2024

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	IV	12/23/2021	None
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	IV	09/23/2022	None
97MG;103MG, 49MG;51MG, 24MG;26MG	7468390	11/27/2023			IV	07/08/2019	Expired
97MG;103MG, 49MG;51MG, 24MG;26MG	7468390*PED	05/27/2024			IV	07/08/2019	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
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	8101659	01/15/2025					None
49MG;51MG, 97MG;103MG, 24MG;26MG	8101659	01/14/2023			IV	07/08/2019	Expired
97MG;103MG, 49MG;51MG, 24MG;26MG	8101659*PED	07/14/2023			IV	07/08/2019	Expired
49MG;51MG, 24MG;26MG, 97MG;103MG	8404744	01/14/2023			IV	07/08/2019	Expired
97MG;103MG, 49MG;51MG, 24MG;26MG	8404744*PED	07/14/2023			IV	07/08/2019	Expired
49MG;51MG, 97MG;103MG, 24MG;26MG	8796331	01/14/2023	U-1723	TREATMENT OF HEART FAILURE	IV	07/08/2019	Expired
97MG;103MG, 49MG;51MG, 24MG;26MG	8796331*PED	07/14/2023			IV	07/08/2019	Expired
97MG;103MG, 49MG;51MG, 24MG;26MG	8877938	05/27/2027			IV	07/08/2019	None
97MG;103MG, 49MG;51MG, 24MG;26MG	8877938*PED	11/27/2027			IV	07/08/2019	None
24MG;26MG, 97MG;103MG, 49MG;51MG	9388134	11/08/2026	U-1723	TREATMENT OF HEART FAILURE	IV	07/08/2019	None
97MG;103MG, 49MG;51MG, 24MG;26MG	9388134*PED	05/08/2027			IV	07/08/2019	None
24MG;26MG, 49MG;51MG, 97MG;103MG	9517226	08/22/2033	U-3084	TREATMENT OF HEART FAILURE WITH PRESERVED EJECTION FRACTION	IV	09/23/2022	None
24MG;26MG, 49MG;51MG, 97MG;103MG	9937143	08/22/2033	U-3084	TREATMENT OF HEART FAILURE WITH PRESERVED EJECTION FRACTION	IV	09/23/2022	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	8101659*PED	07/15/2025					None

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
97MG;103MG, 49MG;51MG, 24MG;26MG	NCE PED	01/07/2021	NEW CHEMICAL ENTITY; PEDIATRIC EXCLUSIVITY	does not intend to market prior to the expiration of the NCE exclusivity	07/08/2019	Expired
49MG;51MG, 97MG;103MG, 24MG;26MG	NPP/S-013	10/01/2022	NEW PATIENT POPULATION			Expired
97MG;103MG, 49MG;51MG, 24MG;26MG	NPP PED	04/01/2023	NEW PATIENT POPULATION; PEDIATRIC EXCLUSIVITY	Seeks approval after expiration	09/23/2022	Expired
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	M-82	02/16/2024	LABELING REVISIONS RELATED TO CLINICAL STUDIES			Expired
49MG;51MG, 97MG;103MG, 24MG;26MG	M-82	02/16/2024	LABELING REVISIONS RELATED TO CLINICAL STUDIES	Seeks approval after expiration.	09/23/2022	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)

Deficiency Comments:

4.4 UNITED STATES PHARMACOPEIA (USP) (C6 ADDENDUM)

The USP was searched on 05/17/2024

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:

N/A.

Deficiency Comments:

4.5 MODEL CONTAINER LABELS (C6 ADDENDUM)

Physician Sample
Not for Sale

Entresto
(sacubitril/valsartan)
tablets

24 mg/26 mg

Rx only
28 Tablets

NOVARTIS

1825772 USS

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.
Mfg. 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

NDC 0078-0777-67

Entresto
(sacubitril/valsartan)
tablets

49 mg/51 mg

Rx only
180 Tablets

NOVARTIS

1826200 US

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.
Mfg. 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

NDC 0078-0696-20

Entresto
(sacubitril/valsartan)
tablets

97 mg/102 mg

Rx only
60 Tablets

NOVARTIS

1826201 US

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.
Mfg. 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

DARRTS; ANRPT-4 submitted 8/30/2019. Note storage is not updated per S-016.


NDC 0078-0659-67

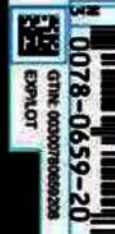
Entresto®
 (sacubitril/valsartan)
 tablets
24 mg/26 mg
 Rx only
 180 Tablets


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.
 Mfg. 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 121253 US

**Physician Sample
 Not for Sale**

Entresto®
 (sacubitril/valsartan)
 tablets
24 mg/26 mg
 Rx only 28 Tablets


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.
 Mfg. 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 0078-9009-50 12112 US


NDC 0078-0659-20

Entresto®
 (sacubitril/valsartan)
 tablets
24 mg/26 mg
 Rx only
 60 Tablets


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.
 Mfg. 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


NDC 0078-0777-67

Entresto®
 (sacubitril/valsartan)
 tablets
49 mg/51 mg
 Rx only
 180 Tablets


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.
 Mfg. 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

**Physician Sample
 Not for Sale**

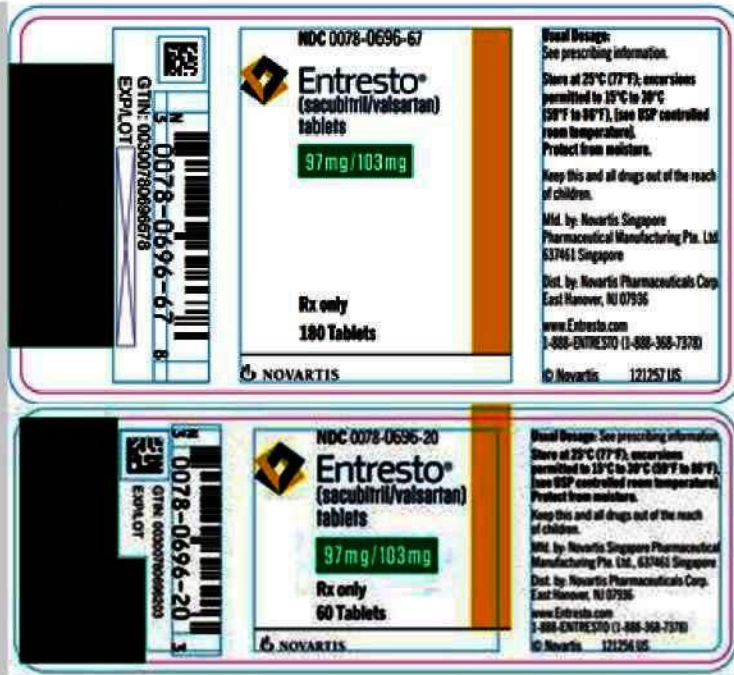
Entresto®
 (sacubitril/valsartan)
 tablets
49 mg/51 mg
 Rx only 28 Tablets


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.
 Mfg. 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 0078-5777-50 121138 US


NDC 0078-0777-20

Entresto®
 (sacubitril/valsartan)
 tablets
49 mg/51 mg
 Rx only
 60 Tablets


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.
 Mfg. 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



Model container/carton/blister labels (Source: DARRTS; ANRPT-3 submitted 8/30/2018). The RLD has delisted blister packs

24 mg / 26 mg

Entresto™
(Sacubitril/Valsartan) Tablets

NDC 079-0529-35

Usual Dosage: See prescribing information.
Store at 20°C (67°F); excursions permitted to 15°C to 30°C (59°F to 86°F) (see USP controlled room temperature). Protect from moisture.

This package is for in-institution use only, as contents are NOT CHILD-RESISTANT. Do not distribute for household use. Keep the unit out of the reach of children.

Mfg. by Novartis Singapore Pharmaceutical Manufacturing Pte. Ltd.
SINGAPORE

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

www.entresto.com
1-800-441-9323 (1-800-441-9323)

1 357-690-23-2

© Novartis 13732-0291

NDC 079-0529-35

Entresto™
(Sacubitril/Valsartan) Tablets
24 mg / 26 mg

Rx only 300 Tablets (30 x 10-Count Unit Dose)

NDC 079-0529-35

Entresto™
(Sacubitril/Valsartan) Tablets
24 mg / 26 mg

Rx only 300 Tablets (30 x 10-Count Unit Dose)

NOVARTIS

49 mg / 51 mg

Entresto™
(Sacubitril/Valsartan) Tablets

NDC 079-0777-35

Usual Dosage: See prescribing information.
Store at 20°C (67°F); excursions permitted to 15°C to 30°C (59°F to 86°F) (see USP controlled room temperature). Protect from moisture.

This package is for in-institution use only, as contents are NOT CHILD-RESISTANT. Do not distribute for household use. Keep the unit out of the reach of children.

Mfg. by Novartis Singapore Pharmaceutical Manufacturing Pte. Ltd.
SINGAPORE

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

www.entresto.com
1-800-441-9323 (1-800-441-9323)

1 357-777-8-001

© Novartis 13732-0291

NDC 079-0777-35

Entresto™
(Sacubitril/Valsartan) Tablets
49 mg / 51 mg

Rx only 300 Tablets (30 x 10-Count Unit Dose)

NDC 079-0777-35

Entresto™
(Sacubitril/Valsartan) Tablets
49 mg / 51 mg

Rx only 300 Tablets (30 x 10-Count Unit Dose)

NOVARTIS

113 mg / 132 mg

Entresto™
(Sacubitril/Valsartan) Tablets

NDC 079-0925-35

Usual Dosage: See prescribing information.
Store at 20°C (67°F); excursions permitted to 15°C to 30°C (59°F to 86°F) (see USP controlled room temperature). Protect from moisture.

This package is for in-institution use only, as contents are NOT CHILD-RESISTANT. Do not distribute for household use. Keep the unit out of the reach of children.

Mfg. by Novartis Singapore Pharmaceutical Manufacturing Pte. Ltd.
SINGAPORE

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

www.entresto.com
1-800-441-9323 (1-800-441-9323)

1 357-925-23-2

© Novartis 13732-0291

NDC 079-0925-35

Entresto™
(Sacubitril/Valsartan) Tablets
113 mg / 132 mg

Rx only 300 Tablets (30 x 10-Count Unit Dose)

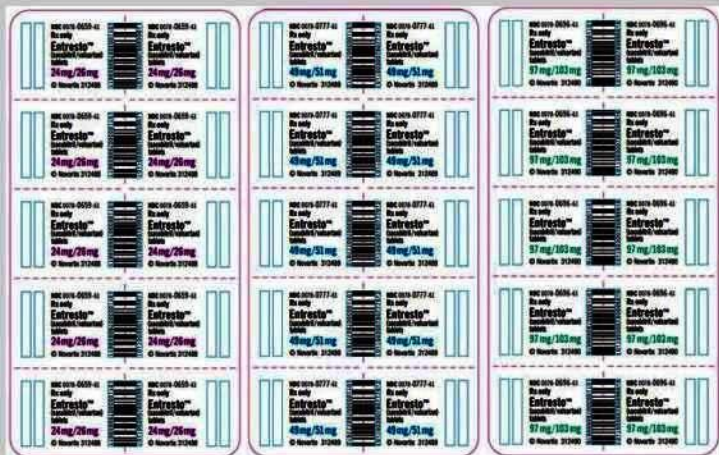
NDC 079-0925-35

Entresto™
(Sacubitril/Valsartan) Tablets
113 mg / 132 mg

Rx only 300 Tablets (30 x 10-Count Unit Dose)

NOVARTIS

Model container/carton/blister labels (Source: DARRTS; ANRPT-1 submitted 8/30/2016). The applicant is no longer marketing blisters container/cartons.



5 ASSESSMENT OF ANDA LABELING AND LABELS (C6 ADDENDUM)

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

5.1.1 DRUG PRODUCT REVIEW (C6 ADDENDUM)

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

R06. 12/14/2023

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	Dimension (mm) (Length x Width)	Imprint Code
24mg/26mg	9.11x 5.08	Violet white color, oval, biconvex film-coated tablets debossed with "S5" on one side and plain on the other side.
49mg/51mg	12.75 x 5.90	Pale yellow color, oval, biconvex film-coated tablets debossed with "S1" on one side and plain on the other side.
97mg/103mg	12.57 x 6.85	Light pink color, oval, biconvex film-coated tablets debossed with "S2" on one side and plain on the other side.

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 (C6 ADDENDUM)

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

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

	ingredients are microcrystalline cellulose, low-substituted hydroxypropyl cellulose, 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). (b) (4)
Previous ANDA Labeling	11 DESCRIPTION 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 crospovidone, low-substituted hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, and silicon dioxide. The film-coat inactive ingredients are hypromellose, titanium dioxide, Macrogol 4000, talc, and iron oxide red. 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. The film-coat for the 49 mg of sacubitril and 51 mg of valsartan tablet contains iron oxide yellow.
Current ANDA Labeling	11 DESCRIPTION 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 crospovidone, low-substituted hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, and silicon dioxide. The film-coat inactive ingredients are hypromellose, titanium dioxide, Macrogol 4000, talc, and iron oxide red. 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. The film-coat for the 49 mg of sacubitril and 51 mg of valsartan tablet contains iron oxide yellow.

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

5/17/2024, C6 Addendum, Labeling Assessment- No changes to inactive ingredients.

5.1.3 HOW SUPPLIED/STORAGE AND HANDLING (C6 ADDENDUM)

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. (b)(4) All strengths are packaged in bottles as described below. <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th colspan="5">ENTRESTO Tablets</th> </tr> <tr> <th rowspan="2">Sacubitril/valsartan mg/mg</th> <th rowspan="2">Color</th> <th rowspan="2">Debossment Side 1/side 2</th> <th colspan="2">NDC 0078-XXXX-XX</th> </tr> <tr> <th>Bottle of 60</th> <th>Bottle of 180</th> </tr> </thead> <tbody> <tr> <td>24/26</td> <td>Violet white</td> <td>NVR/LZ</td> <td>0659-20</td> <td>0659-67</td> </tr> <tr> <td>49/51</td> <td>Pale yellow</td> <td>NVR/L1</td> <td>0777-20</td> <td>0777-67</td> </tr> <tr> <td>97/103</td> <td>Light pink</td> <td>NVR/L11</td> <td>0696-20</td> <td>0696-67</td> </tr> </tbody> </table> (b)(4)	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
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																								
Previous ANDA Labeling	C5, 16 HOW SUPPLIED/STORAGE AND HANDLING Sacubitril and valsartan tablets are available as described below: Sacubitril and valsartan tablets 24/26 mg, (sacubitril 24 mg and valsartan 26 mg) are violet white color, oval shaped, biconvex film-coated tablets debossed with “S5” on one side and plain on the other side. Bottles of 30 NDC 42385-930-30 Bottles of 60 NDC 42385-930-60 Bottles of 180 NDC 42385-930-18 Carton with 100 (10 x 10) Unit-Dose Tablets containing cold form with desiccant blisters NDC 42385-930-68 Carton with 100 (10 x 10) Unit-Dose Tablets containing PVC/ACLAR blisters NDC 42385-930-72 Sacubitril and valsartan tablets 49/51 mg, (sacubitril 49 mg and valsartan 51 mg) are pale yellow color, oval shaped, biconvex film-coated tablets debossed with “S1” on one side and plain on the other side. Bottles of 30 NDC 42385-931-30 Bottles of 60 NDC 42385-931-60 Bottles of 180 NDC 42385-931-18 Carton with 100 (10 x 10) Unit-Dose Tablets containing cold form with desiccant blisters NDC 42385-931-68 Carton with 100 (10 x 10) Unit-Dose Tablets containing PVC/ACLAR blisters NDC 42385-931-72																											

Table 8: Comparison of Model Labeling to ANDA Labeling

	Sacubitril and valsartan tablets 97/103 mg, (sacubitril 97 mg and valsartan 103 mg) are light pink color, oval shaped, biconvex film-coated tablets debossed with “S2” on one side and plain on the other side. Bottles of 30 NDC 42385-932-30 Bottles of 60 NDC 42385-932-60 Bottles of 180 NDC 42385-932-18 Carton with 100 (10 x 10) Unit-Dose Tablets containing cold form with desiccant blisters NDC 42385-932-68 Carton with 100 (10 x 10) Unit-Dose Tablets containing PVC/ACLAR blisters NDC 42385-932-72 Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature]. Protect from moisture.
Current ANDA Labeling	C6, 16 HOW SUPPLIED/STORAGE AND HANDLING Sacubitril and valsartan tablets are available as described below: Sacubitril and valsartan tablets 24/26 mg, (sacubitril 24 mg and valsartan 26 mg) are violet white color, oval shaped, biconvex film-coated tablets debossed with “S5” on one side and plain on the other side. Bottles of 30 NDC 42385-930-30 Bottles of 60 NDC 42385-930-60 Bottles of 180 NDC 42385-930-18 Carton with 100 (10 x 10) Unit-Dose Tablets containing cold form with desiccant blisters NDC 42385-930-68 Carton with 100 (10 x 10) Unit-Dose Tablets containing PVC/ACLAR blisters NDC 42385-930-72 Sacubitril and valsartan tablets 49/51 mg, (sacubitril 49 mg and valsartan 51 mg) are pale yellow color, oval shaped, biconvex film-coated tablets debossed with “S1” on one side and plain on the other side. Bottles of 30 NDC 42385-931-30 Bottles of 60 NDC 42385-931-60 Bottles of 180 NDC 42385-931-18 Carton with 100 (10 x 10) Unit-Dose Tablets containing cold form with desiccant blisters NDC 42385-931-68 Carton with 100 (10 x 10) Unit-Dose Tablets containing PVC/ACLAR blisters NDC 42385-931-72 Sacubitril and valsartan tablets 97/103 mg, (sacubitril 97 mg and valsartan 103 mg) are light pink color, oval shaped, biconvex film-coated tablets debossed with “S2” on one side and plain on the other side. Bottles of 30 NDC 42385-932-30 Bottles of 60 NDC 42385-932-60 Bottles of 180 NDC 42385-932-18 Carton with 100 (10 x 10) Unit-Dose Tablets containing cold form with desiccant blisters NDC 42385-932-68

Table 8: Comparison of Model Labeling to ANDA Labeling

	Carton with 100 (10 x 10) Unit-Dose Tablets containing PVC/ACLAR blisters NDC 42385-932-72 Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature]. Protect from moisture. 5/17/2024, C6 Addendum, Labeling Assessment- No changes.

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

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

Previous ANDA Labeling	
Name and Address on ANDA Prescribing Information	(b)(4)
Current ANDA Labeling	
Name and Address on ANDA Prescribing Information	(b)(4)

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 ADDENDUM)

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).

Deficiency	No Deficiency	
☐	☒	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:		
Containers and U/D labels were satisfactory during previous cycles on submission dates indicated as follows:		
(b) (4)		
Deficiency Comments:		

5.2.1 UNIT-DOSE BLISTERS(C6 ADDENDUM)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Each blister contains only one dosage unit (e.g. one tablet, one capsule).
☐	☒	Established/proprietary name, strength, bar code, and manufacturer/distributor/packer appear accurately on each blister cell.
Reviewer Comments:		
Satisfactory in the previous cycle (2).		

Deficiency Comments:

5.3 CARTON (OUTER OR SECONDARY PACKAGING) LABELING (C6 ADDENDUM)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☐	Unit-Dose Carton expression of strength appropriately stated.
☐	☒	The answers to the Container Label questions are the same for the Carton Labeling. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

U/D carton labels are satisfactory in the 11/26/2021 submission.

Deficiency Comments:

5.4 PRESCRIBING INFORMATION (C6 ADDENDUM)

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.
☐	☒	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:		

Deficiency	No Deficiency	
☐	☒	<u>STIC</u> 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:

(b) (4)

5/17/2024 Adequate PI and PPI labeling submitted 5/15/2024

Deficiency Comments:

5.5 OTHER PATIENT LABELING (C6 ADDENDUM)

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 Addendum 5/17/2024: Satisfactory PPI in the 5/15/2024 submission.		
Deficiency Comments:		

6 COMMENTS/CONSULTS FOR OTHER DISCIPLINES (C6 ADDENDUM)

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:



Angela
Payne

Digitally signed by Angela Payne
Date: 5/20/2024 02:06:50PM
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Burhan
Nour

Digitally signed by Burhan Nour
Date: 5/21/2024 09:40:41PM
GUID: 508da70600028ae6e75df33aa0f5b2ce

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 213676

CHEMISTRY REVIEW(s)

ANDA Executive Summary

1. Application/Product Information

ANDA Number.	213676
Review Cycle #	6
Applicant Name	Laurus Labs Limited
Drug Product Name	Sacubitril and Valsartan Tablets 24 mg/26 mg. 49 mg/51 mg and 97 mg/ 103 mg
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 sodium 194mg; Valsartan disodium 206 mg
Rx/OTC Dispensed	Rx
Proposed Indication	(b)(4)
Drug Product Description	24 mg/26 mg: Violet white color, oval shaped, biconvex film-coated tablets debossed with "S5" on one side and plain on the other side. 49 mg/51 mg: Pale yellow color, oval shaped, biconvex film-coated tablets debossed with "S1" on one side and plain on the other side. 97 mg/103 mg: Light pink color, oval shaped, biconvex film-coated tablets debossed with "S2" on one side and plain on the other side
Co-packaged product information	N/A

Device information, if any:	N/A		
Storage Temperature/ Conditions	20°C to 25°C		
Review Team	Discipline	Primary	Secondary
	<i>Drug Substance</i>	Xihong Wang/ Xianru Sun	Marco A. Bennett/ Erin Skoda
	<i>Drug Product/ Labeling</i>	Xihong Wang	Marco A. Bennett
	<i>Manufacturing</i>	Mirtha Millones / Md Abdullah Mahmud	Bo Jiang / Zhaoyang Meng
	<i>Biopharmaceutics</i>	Churg Chan	Om Anand
	<i>Microbiology</i>	N/A	N/A
	<i>Other (specify):</i>	N/A	N/A
	<i>RBPM</i>	Ify Mordi	
	<i>ATL</i>	Marco A. Bennett	
Consults	Discipline Consulted	Recommendation	Date
	N/A	N/A	N/A

2. Submission Document(s) Reviewed

Submission(s) Assessed	Documents Date	Disciplines Affected
Original/Initial Submission	07/08/2019	Quality
Quality/Response to Information Request	09/16/2019	Quality
Quality/Response to Discipline Review Letter	02/06/2020	Quality
Quality/Response to Information Request	03/02/2020	Quality

Resubmission/After Action- Complete	07/01/2020	Quality
Resubmission/After Action- Complete	05/03/2021	Quality
Amendment	08/02/2021	Quality
Resubmission/After Action- Complete	11/26/2021	DP
Resubmission/After Action- Complete	03/17/2022	DP, MFG
Gratuitous Amendment (Subject of Labeling review)	09/23/2022	Labeling
Gratuitous Amendment (Subject of review #6)	11/18/2022	DP
Resubmission/After Action- Complete	05/15/2023	DP
Quality/Response to Information Request	06/12/2023	Process

3. Related/Supporting Documents

a. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Assessor/ Comments
33647	II	Laurus Labs Limited	Sacubitril-Valsartan 3Na Complex	Inadequate	12/14/2023	Xianru Sun

b. Other Documents: IND, RLD, RS, Approved ANDA

Document	Application Number	Description
NDA (RLD)	NDA 207620	ENTRESTO® (sacubitril and valsartan) tablets 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg, manufactured by (b)(4) (b)(4) Approval date: 07/07/2015

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.*)

1. None

Drug Substance Deficiencies

1. None

Drug Product Deficiencies

1. None

Labeling Deficiencies (*Please contact OGD if you identify any Labeling deficiencies with your comments*)

1. None

Manufacturing Deficiencies

1. None

Biopharmaceutics Deficiencies

1. None

Microbiology Deficiencies

1. None

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. None

Additional Comments:

In addition to responding to the deficiencies presented above, please note and acknowledge the following comment(s) in your response: None

5. Basis for Recommendation

a. Summary of Rationale for Recommendation:

OPQ recommends approval of this ANDA on the basis that OLDP (CMC), Process, Microbiology and Facilities are all adequate a summary paragraph outlining reasons for OPQ action recommendation.

NDSRI Impacted Application: No
If yes, Risk Mitigated? NA

b. Recommendation by Subdiscipline:

Drug Substance: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view [Justification Statements](#))

1. N/A

Drug Product: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view [Justification Statements](#))

1. N/A

Quality Labeling: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view [Justification Statements](#))

1. N/A

Manufacturing: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view [Justification Statements](#))

1. N/A

Biopharmaceutics: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view [Justification Statements](#))

1. N/A

Microbiology: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view [Justification Statements](#))

1. N/A

Environmental: N/A

Provide justification(s) (for major deficiencies only):
(Click link to view [Justification Statements](#))

1. N/A

6. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments: None

Comparability Protocols (PACMP): No
Comments: None

Additional Comments: None



Marco A.
Bennett

Digitally signed by Marco A. Bennett
Date: 12/15/2023 02:16:59PM
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DRUG PRODUCT QUALITY ASSESSMENT

ANDA 213676 (Review Cycle # 06)

Sacubitril and Valsartan Tablets,

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

Xihong Wang

Division of Immediate Release Products I/Branch II

Office of Lifecycle Drug Products

Office of Pharmaceutical Quality

Notes:

-

-

(b) (4)

NDSRI Impacted Application: No
If yes, Risk Mitigated? NA

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ANDA 213676 (Assessment Cycle # 06)

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	Laurus Labs Limited Second Floor, Serene Chambers, Road No.7, Banjara Hills Hyderabad, Telangana India, 500034	
Drug Product Manufacturer	☐ Same as the Applicant ☒ Different from the Applicant (see below)	
	(b)(4)	
US agent, if applicable	☐ N/A ☒ (See Below) Sharath Koripally, Senior Director RA, QA & PV Laurus Generics Inc. 400 Connell Drive, Suite 5200 Berkeley Heights, NJ 07922 Tel: (718) 510-6822 Email: sharath.koripally@laurusgenerics.com	
Proposed Indication	(b)(4)	

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original (Subject of review #1)	07/08/2019	All
Amendment: Response to DRL-Labeling dated 10/25/19 (Subject of review #1)	11/07/2019	Labeling
Amendment: Response to DRL-Labeling dated 01/03/20 (Subject of review #1, IR#1)	02/06/2020	DP, Biopharm, Process
Amendment: Response to IR letter from the agency (Biopharm) dated 02/20/2020 (Subject of Biopharm review)	03/02/2020	Biopharm
Amendment: Response to CR letter from the agency dated 05/04/2020 (Subject of review #2)	07/01/2020	DP, Facility, BE
Amendment: Response to CR letter from the agency dated 02/22/2021 (Subject of review #3)	05/03/2021	DP, Labeling
General Correspondence: Change in US agent (Updated in the table above)	08/02/2021	
Amendment: Response to CR letter from the agency dated 10/04/2021 (Subject of Labeling review)	11/26/2021	Labeling
Amendment: Response to CR letter from the agency dated 02/23/2022 (Subject of review #5)	03/17/2022	DP, Labeling
Gratuitous Amendment (Subject of Labeling review)	09/23/2022	Labeling

Gratuitous Amendment (Subject of review #6)	11/18/2022	DP
Amendment: Response to CR-Major letter from the agency dated 12/10/2022 (Subject of review #6)	05/15/2023	DP
Amendment: Response to IR letter from the agency dated 06/08/2023 (Subject of process review)	06/12/2023	Process

QUALITY ASSESSMENT DATA SHEET

IQA ANDA Assessment Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Reviewed	Comments
33647	II	Laurus Labs Limited	Sacubitril-Valsartan 3Na Complex	Adequate	12/14/2023	Xianru Sun
Other DMF: ☐ N/A ☒ (See Below)						
(b)(4)	III	(b)(4)	(b)(4)			
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	IV					

			(b)(4)			

B. OTHER DOCUMENTS: IND, RLD, RS, Approved ANDA

Document	Application Number	Brand Name	Description
NDA (RLD)	NDA 207620	ENTRESTO® (sacubitril and valsartan) tablets	ENTRESTO® (sacubitril and valsartan) tablets 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg, manufactured by (b)(4) (b)(4) Approval date: 07/07/2015

2. CONSULTS: None

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology				
CDRH-ODE				
CDRH-OC				
Clinical				
Other				

30 Pages have been withheld in full as b4 (CCI/TS) immediately following this page

CHAPTER I: DRUG SUBSTANCE

[IQA ANDA Assessment Guide Reference](#)

Drug Substance Name	Sacubitril-Valsartan 3Na Complex
DMF Number (If Applicable)	033647
DMF Status	Inadequate - Major
DMF Holder	Laurus Labs Limited

Overall Assessment Recommendation for DS:

DRL

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.

Highlight Key Issues from Last Cycle and Their Resolution:

N/A - This is the review of original ANDA

Concise Description of Outstanding Issues:

Choose an item.

Select Number of Approved Comparability Protocols: 0

S.1 GENERAL INFORMATION

Nomenclature/Chemical name	:	Tri sodium [3-((1 <i>S</i> ,3 <i>R</i>)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl -1-butylcarbamoyl)propionate-(<i>S</i>)-3'-methyl-2'-(pentanoyl {2''-(tetrazol-5-ylate) biphenyl-4'-ylmethyl} amino)butyrate] (or) Tri sodium (4-[[[(1 <i>S</i> ,3 <i>R</i>)-1-([1,1'-biphenyl-4-ylmethyl-4-ethoxy-3-methyl-4-oxobutyl]amino)-4-oxobutanoate)(N-pentanoyl-N-{2'-(1 <i>H</i> -tetrazol-1-id-5-yl) [1,1'-biphenyl]-4-yl]methyl}-L-valinate)			
		<table border="1"> <thead> <tr> <th>Sacubitril</th> <th>Valsartan</th> </tr> </thead> <tbody> <tr> <td>4-[[[(1<i>S</i>,3<i>R</i>)-1-([1,1'-Biphenyl] -4-ylmethyl)-4-ethoxy -3-methyl-4-oxobutyl]amino]-4-oxobutanoic acid</td> <td>N-Pentanoyl-N-{[2'-(1<i>H</i>-tetrazol-5-yl)[1,1'-biphenyl] -4-yl]methyl}-L-valine</td> </tr> </tbody> </table>	Sacubitril	Valsartan	4-[[[(1 <i>S</i> ,3 <i>R</i>)-1-([1,1'-Biphenyl] -4-ylmethyl)-4-ethoxy -3-methyl-4-oxobutyl]amino]-4-oxobutanoic acid
Sacubitril	Valsartan				
4-[[[(1 <i>S</i> ,3 <i>R</i>)-1-([1,1'-Biphenyl] -4-ylmethyl)-4-ethoxy -3-methyl-4-oxobutyl]amino]-4-oxobutanoic acid	N-Pentanoyl-N-{[2'-(1 <i>H</i> -tetrazol-5-yl)[1,1'-biphenyl] -4-yl]methyl}-L-valine				
International Non-proprietary Name (INN)	:	Not reported			
Compendial Name (WHO)	:	Not reported			
United States Adopted Name (USAN)	:	Sacubitril and valsartan			
Molecular Structure	:	Sacubitril-Valsartan 3Na Complex			
Molecular Formula	:	C ₄₈ H ₅₅ N ₆ O ₈ .3Na			
CAS number	:	936623-90-4			
Relative Molecular mass	:	912.95			
Pharmacological Class	:	(b)(4)			

Physical form	:	White to off-white solid
Solubility	:	Soluble in methanol, practically insoluble in cyclohexane.

Updates in review #3 as per AM dated 05/03/2021 are in light Blue
Updates in review #6 as per AM dated 05/15/2023 are in dark red

Applicable ICH Identification and Qualification thresholds:

MDD	ICH Identification threshold	ICH Qualification threshold
(b)(4)	0.10%	0.15%
	0.10%	0.15%

Listing of related substances in DS:

13 Pages have been withheld in full as b4 (CCI/TS) immediately following this page



(b) (4)

Post-Approval Stability Protocol and Commitment

Please refer to DMF # 033647 of Sacubitril- Valsartan 3Na Complex drug substance for information on Post-Approval Stability Protocol and Stability Commitment.

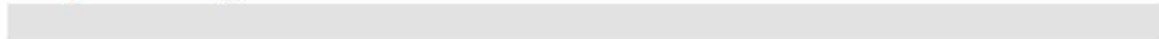
Assessment: Choose an item.
N/A

R REGIONAL INFORMATION

Comparability Protocols N/A (See Below)

Assessment: Choose an item.

Lifecycle Management Considerations



DRUG SUBSTANCE LIST OF DEFICIENCIES:

1. 
2. 
3. 
4. 

(b) (4)

CHAPTER II: DRUG PRODUCT

[IQA ANDA Assessment Guide Reference](#)

Overall Assessment Recommendation: Discipline Review Letter (DRL)

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:

Drug Product CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Review Cycle #2	Comments*
Physical stability (solid state)	36 Medium	(b)(4)	Low	(b)(4)
Chemical Stability	48 Medium		Low	
Assay	18 Low		Low	
Content uniformity	24 Low			

		(b)(4)		(b)(4)
Microbial limits	9 Low		Low	
Dissolution	48 Medium			

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 the 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. Biopharm review is inadequate.*
- *Elemental impurity compliance with ICH Q3D – status: Adequate*
- *Number of Comparability protocols included: 0*

RLD versus Generic Product – NOT FOR FOIA

(b) (4)

* For repacking purpose only

P.1 DESCRIPTION AND COMPOSITION

Component/Composition of Sacubitril and Valsartan Tablets 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg

Ingredients	Compendial Reference	Pharmaceutical Function	24mg/26mg	49mg/51mg	97mg/103mg	%w/w
			(mg/ Tablet)			
(b)(4)						
Sacubitril-Valsartan 3Na Complex [^]	In-House	Active Ingredient	(b)(4)			
Low-substituted hydroxypropylcellulose (b)(4)	USP-NF	(b)(4)				
Microcrystalline Cellulose (b)(4)	USP-NF					
Crospovidone (b)(4)	USP-NF					
(b)(4)						
Silicon dioxide (b)(4)	USP-NF					
(b)(4)						
Magnesium Stearate (b)(4)	USP-NF					
(b)(4)						
(b)(4)						
(b)(4)						
(b)(4)						
(b)(4)						
Weight of Coated Tablet			103.000	206.000	412.000	100.000
(b)(4)						

Comparison of ingredients used between the formulation of the RLD and the proposed generic drug product is provided in the Table below.

Comparison of Ingredients used in RLD and Proposed Drug Product

Proposed Generic Drug Product	Reference Listed Drug (Entresto) TM	Pharmaceutical Function
Sacubitril-Valsartan 3Na Complex	Sacubitril-Valsartan 3Na • 2½ H ₂ O Complex	Active Ingredient
Low-substituted hydroxypropylcellulose	Low-substituted hydroxypropylcellulose	(b)(4)
Microcrystalline Cellulose	Microcrystalline Cellulose	
Crospovidone	Crospovidone	
Silicon dioxide	(b)(4)	
(b)(4)	Colloidal silicon dioxide	
	Talc	
Magnesium Stearate	Magnesium Stearate	
(b)(4)	(b)(4)	
Hypromellose [®] (b)(4)	Hypromellose	
Titanium Dioxide [®]	Titanium Dioxide	
(b)(4)	Macrogol 4000	
Talc [®]	Talc	
(b)(4)	Iron oxide Yellow	
	Iron oxide black	
	(b)(4)	

(b)(4)

(b)(4)

R REGIONAL INFORMATION

Environmental

- Laurus Labs Limited states that for this Abbreviated New Drug Application (ANDA) we are subject to a categorical exclusion from the requirement to prepare an Environmental Assessment Statement, as per 21 CFR § 25.30, 25.31, 25.33 and 25.15 (d).
- This ANDA is for the drug product which will not be indicated for administration at a higher dose level, nor for a longer duration, or for different indications than those that are in effect. No extraordinary circumstances, as outlined in 21 CFR § 25.21, exist. Hence, a categorical exclusion from the requirement to prepare an Environmental Assessment is hereby requested.
- Also, Laurus Labs Limited, hereby states that we are in compliance with all federal, state and local environmental laws.

Assessment:
Adequate

Adequate

Methods Validation or Verification Package

Assessment:

Adequate

Comparability Protocols

Assessment:
N/A

Choose an item.

Lifecycle Management Considerations

DRUG

1.

(b) (4)

2.

3.

4.

(b) (4)

5.

(b) (4)

6.

7.

CHAPTER III: ENVIRONMENTAL

[IQA ANDA Assessment Guide Reference](#)

R REGIONAL INFORMATION

Environmental

- Laurus Labs Limited states that for this Abbreviated New Drug Application (ANDA) we are subject to a categorical exclusion from the requirement to prepare an Environmental Assessment Statement, as per 21 CFR § 25.30, 25.31, 25.33 and 25.15 (d).
- This ANDA is for the drug product which will not be indicated for administration at a higher dose level, nor for a longer duration, or for different indications than those that are in effect. No extraordinary circumstances, as outlined in 21 CFR § 25.21, exist. Hence, a categorical exclusion from the requirement to prepare an Environmental Assessment is hereby requested.
- Also, Laurus Labs Limited, hereby states that we are in compliance with all federal, state and local environmental laws.

Assessment:
Adequate

Adequate

CHAPTER IV: LABELING

[IQA ANDA Assessment Guide Reference](#)

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	Dimension (mm) (Length x Width)	Imprint Code
24mg/26mg	9.11x 5.08	Violet white color, oval, biconvex film-coated tablets debossed with "S5" on one side and plain on the other side.
49mg/51mg	12.75 x 5.90	Pale yellow color, oval, biconvex film-coated tablets debossed with "S1" on one side and plain on the other side.
97mg/103mg	12.57 x 6.85	Light pink color, oval, biconvex film-coated tablets debossed with "S2" on one side and plain on the other side.

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

A. Drug Substance Deficiencies

None

B. Drug Product Deficiencies

None

C. Labeling Deficiencies

None

(END OF DRUG PRODUCT QUALITY ASSESSMENT)

Signature Block:

Primary DP Assessor: *Xihong Wang*

Date: 12/19/19;
3/31/2020;
1/22/2021
7/1/2021,
09/16/2021;
01/27/2022,
02/04/2022;
11/08/2022,
12/07/2022;
12/06/2023,
12/14/2023

Secondary DP Assessor: *Marco Bennett*

Date: 12/19/2019;
04.01.2020;
04.14.2020;
01.22.2021;
07.02.2021;
09.17.2021;
01.31.2022;
02.04.2022;
12.08.2022;
12.14.2023



Xihong
Wang

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Marco A.
Bennett

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Date: 12/14/2023 04:57:20PM
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MANUFACTURING INTEGRATED ASSESSMENT

Application ID	ANDA 213676
Drug Product Name	Sacubitril and Valsartan Tablets
Strengths	24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg
Dosage Form	Tablets
Administration Route	Oral
Indication	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	Laurus Labs Limited
RLD Number	207620

I. Manufacturing Summary**Facility Assessment Recommendation: Adequate****Process Assessment Recommendation: Adequate****Assessment Summary:**

Sacubitril and Valsartan Tablets 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg is manufactured using (b)(4)

(b)(4)

List Submissions being assessed (Table):

Document Description (SD #)	Date Received
Original (SD# 0001)	07/08/2019
Response to IR (SD# 0003)	09/16/2019
Response to IR (SD#0007)	02/06/2020
Response to IR (SD#0008)	03/02/2020
Response to CR (SD#0009)	07/01/2020

Highlight Key Issues from Last Cycle and Their Resolution: 1st Cycle**Review #1**

(b)(4)

(b)(4)

Review #2

(b)(4)

Concise Description of Outstanding Issues (List bullet points with key information and update as needed):

- None

List Number of Comparability Protocols: None

1. Lifecycle Management Considerations

Post-approval inspection?	No
Lifecycle considerations	No
Choose an item.	

2. Facilities Table

Facility name and address	FEI	Responsibilities and profile code(s)	Status
Laurus Labs Limited, (VSP-2) (DRUG PRODUCT MANUFACTURER) Plot No. 19, 20 and 21, Western Sector, APSEZ, Atchutapuram, Visakhapatnam, Andhra Pradesh, India, 531011	3011538548	(b)(4)	Approve - Based on Previous History
Laurus Labs Limited (VSP-1) [Drug Substance manufacturer for Sacubitril-Valsartan 3Na Complex] Plot No. 21, Jawaharlal Nehru Pharma City Parawada, Visakhapatnam, Andhra Pradesh, India, 531021	3007083664		Approve - Based on PAI
Laurus Labs Limited (VSP-3) Plot No. 18, Jawaharlal Nehru Pharma City Parawada, Visakhapatnam, Andhra Pradesh, India, 531021	3007083664		Approve - Based on Previous History
(b)(4)			Approve - Based on PAI

(b) (4)	(In lieu of PAI, documents assessed using 704(a)(4))
	(b)(4)
	Approve - Based on PAI (In lieu of PAI, documents assessed using 704(a)(4))





V. List of Outstanding Information Request/Deficiencies:

Outstanding Deficiencies Collation Table	
None	

VI. Signature Block

Round#	Primary Name	Secondary & Other Names	Date of Completion	Assessment Outcome	Facility OMIR
1	Mesfin Abdi 11/12/2019	Jean Tang 12/04/2019	12/5/2019	IR	Withheld
2	Mesfin Abdi 02/13/2020	Jean Tang 02/19/2020	2/19/2020	IR	Withheld
3	Mesfin Abdi 03/03/2020 04/28/2020	Jean Tang 03/13/2020 04/29/2020	4/29/2020	Adequate	Withheld



QUALITY ASSESSMENT



4	Mesfin Abdi 12/18/2020	Jean Tang 12/23/2020	12/23/2020	Adequate	Approve



Mesfin
Abdi

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Jean
Tang

Digitally signed by Jean Tang
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GUID: 502d1ab500002aff2e492acb1fd0d645

BIOPHARMACEUTICS ANDA REVIEW	
Application No.	ANDA-213676-ORIG-1
Applicant	Laurus Labs Limited
Product Name/ Strength(s)	Sacubitril and Valsartan Tablets/ 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg
Dosage Form/Route	Immediate-Release Tablets/Oral
Indication	Reduce the risk of cardiovascular death and hospitalization for heart failure
Submission Date(s)	7/8/2019 – Original Submission 2/6/2020 – Response to Information Request
RLD/RS	Entresto® Tablets [N207620]
Primary Reviewer	Churg Chan, Pharm.D.
Secondary Reviewer	Om Anand, Ph.D.
Recommendation	Adequate

EXECUTIVE SUMMARY:

This Biopharmaceutics Review evaluates data supporting the adequacy of the proposed dissolution method and acceptance criteria for quality control testing of the proposed drug product.

Dissolution Method:

(b)(4)

Based on the provided information and data, the proposed dissolution method (Table 1) is deemed adequate for quality control testing of the proposed product. The Applicant’s originally proposed dissolution acceptance criteria were (b)(4) and therefore not acceptable. Based on the provided data, the Applicant was recommended via an Information Request dated January 3, 2020 to revise the dissolution acceptance criteria to (b)(4)

(b)(4) and “NLT (b)(4) % (Q) of Sacubitril and Valsartan in 30 minutes” for the 49 mg/51 mg and 97 mg/103 mg strengths of the proposed drug product. In a response dated February 6, 2020, the Applicant accepted the FDA recommendation regarding the dissolution acceptance criterion for the 49 mg/51 mg and 97 mg/103 mg strengths, however, they proposed “NLT (b)(4) % (Q) of Sacubitril and Valsartan in 30 minutes” for the 24 mg/26 mg strength as well. Based on the totality of the information/data submitted, the newly proposed dissolution acceptance criterion and the response is acceptable.

¹ [FDA Recommended Dissolution Methods](#)

Table 1. Approved dissolution method and acceptance criteria²

Method Source	USP Apparatus	Speed	Medium	Volume/ Temperature	Recommended Acceptance Criteria
FDA – Database	II (Paddle)	50 RPM	pH 6.8 Phosphate Buffer	900 mL/ 37 ± 0.5°C	NLT $\frac{1}{100}$ % (Q) of Sacubitril in 30 minutes NLT $\frac{1}{100}$ % (Q) of Valsartan in 30 minutes

Recommendation:

From a Biopharmaceutics perspective, ANDA 213676 for the proposed Sacubitril/Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg, is recommended for **approval**.

² [Application 213676 - Sequence 0001 - Pharmaceutical Development Report](#)

BIOPHARMACEUTICS REVIEW**1. Drug Substance Solubility:**

(b)(4)

2. Formulation: The proposed product (b)(4)

(b)(4)

3. Bioequivalence: The Applicant performed *in vivo* pharmacokinetic studies using the 97 mg/103 mg strength of the proposed and RLD products in both fasting and fed conditions.⁶ Under fasting conditions, the T_{max} of Sacubitril and Valsartan were 0.71 and 2.14 hours, respectively.⁷ Under fed conditions, the T_{max} of Sacubitril and Valsartan were 1.83 hours and 3.31 hours, respectively.⁸ The Division of Bioequivalence/OGD will evaluate the bioequivalence study results and the biowaiver request.

4. Dissolution Method: The Applicant proposes to use the same dissolution method for Sacubitril/Valsartan tablets as previously described in the FDA's dissolution database (Table 1).⁹

The Applicant evaluated discriminating ability of the proposed dissolution method on changes of high-risk formulation variables (b)(4)

(b)(4)

The Applicant manufactured batches with (b)(4)

(b)(4)

(b)(4)

The dissolution profiles were similar across the formulations evaluated with the proposed dissolution method. However, based on the totality of the provided data and information, the proposed dissolution method is deemed adequate for quality control testing of the proposed product.

In an Information Request dated January 3, 2020, the Applicant was asked to submit dissolution data (b)(4)

³ [Application 213676 - Sequence 0001 - Quality Overall Summary - Drug Substance \(PDF\)](#)

⁴ [Application 213676 - Sequence 0001 - Description of Manufacturing Process and Process Controls](#)

⁵ [Application 213676 - Sequence 0001 - Description and Composition of the Drug Product](#)

⁶ [Application 213676 - Sequence 0001 - Tabular Listing of All Clinical Studies \(Pivotal Batch\)](#)

⁷ [Application 213676 - Sequence 0001 - Clinical Study Report Body - Fasting Study](#)

⁸ [Application 213676 - Sequence 0001 - Clinical Study Report Body - Fed Study](#)

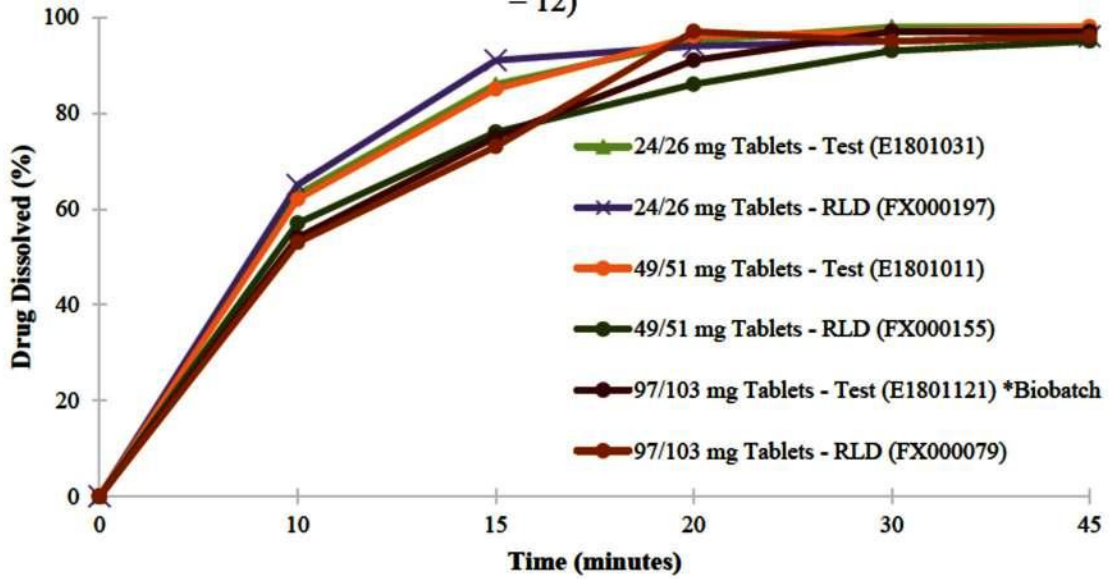
(b)(4)

(b)(4)

(b)(4) The Applicant proposed to continue using their original dissolution method for their proposed drug product [900 mL of pH 6.8 phosphate buffer using USP Apparatus II (Paddle) at 50 rpm].

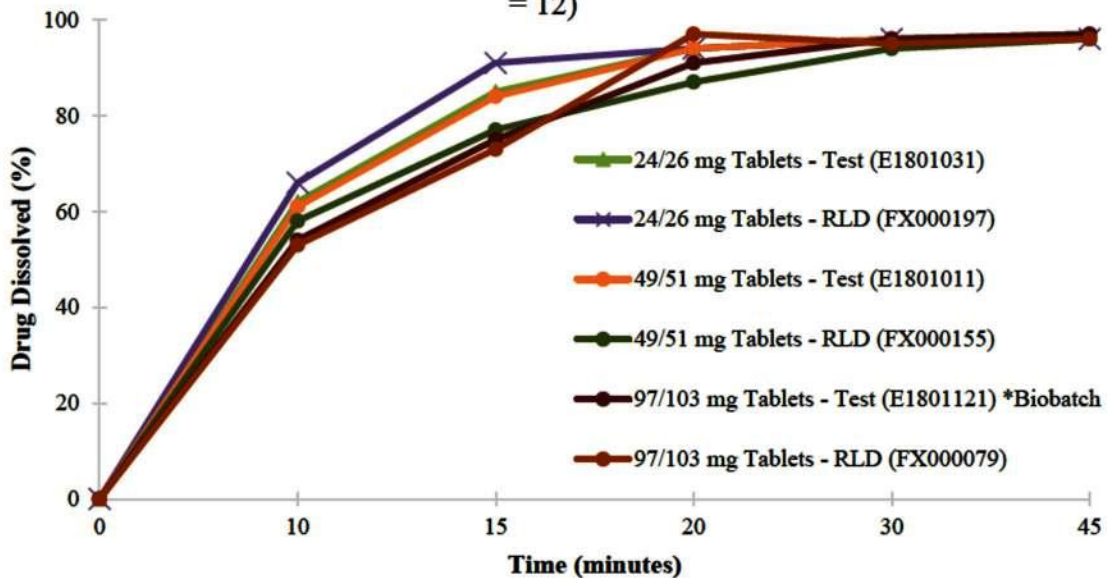
5. Dissolution Data:¹¹

Figure 1. Summary of mean *in vitro* dissolution data for Sacubitril (*n* = 12)



(b)(4)
¹¹ [Application 213676 - Sequence 0001 - Clinical Summary \(PDF\)](#)

Figure 2. Summary of mean *in vitro* dissolution data for Valsartan (*n* = 12)



- 6. Dissolution Acceptance Criteria:** The original dissolution acceptance criteria proposed by the Applicant, (b)(4) was (b)(4) and not supported by the data. The Applicant was recommended via an Information Request dated January 3, 2020 to implement the dissolution acceptance criteria of (b)(4) (b)(4) and “NLT (b)(4)% (Q) of Sacubitril and Valsartan at 30 minutes” for the 49 mg/51 mg and 97/103 mg strength tablets for the proposed drug product. In a response dated February 6, 2020, the Applicant accepted the FDA recommendation regarding the dissolution acceptance criterion for the 49 mg/51 mg and 97 mg/103 mg strengths, however, they proposed “NLT (b)(4)% (Q) of Sacubitril and Valsartan in 30 minutes” for the 24 mg/26 mg strength as well. The Applicant justified their proposition by reviewing data at (b)(4) and 30 minutes for all their exhibit batches and the RLD. Both the proposed and reference drug product have individual unit values (b)(4) than (b)(4)% at the (b)(4) (b)(4) time point, but this trend was not observed at the 30-minute time point. Therefore, based on the totality of the provided data and information, the Applicant’s proposed acceptance criteria are acceptable.
- 7. Stability:** The Applicant provided stability data for exhibit batches of Sacubitril and Valsartan tablets for 6 months under long-term (25° ± 2°C/60% ± 5% RH) and accelerated (40° ± 2°C/75% ± 5% RH) conditions.¹² No significant changes in dissolution in stability were observed using the proposed dissolution method.
- 8. Dissolution Risk/Mitigation Assessment:** The biopharmaceutics and dissolution risk are relatively high because Sacubitril and Valsartan are considered (b)(4) per the

¹² [Application 213676 - Sequence 0001 - Stability Summary and Conclusion](#)

Applicant's BCS claims. The dissolution acceptance criteria are adequately selected to mitigate the risk of dissolution failure for the proposed drug product.

Biopharmaceutics Information Request

The following Biopharmaceutics Information Request (IR) comments were conveyed to the Applicant on January 3, 2020:

1. Based on the provided information and data, the proposed dissolution method (USP II at 50 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 (b)(4) dissolution acceptance criteria and therefore the proposed acceptance criterion is not acceptable. Implement the following acceptance criteria for your proposed product, Sacubitril and Valsartan Tablets:

Sacubitril and Valsartan Tablets, 24 mg/26 mg strength

(b)(4)

Sacubitril and Valsartan Tablets 49 mg/51 mg and 97/103 mg strengths

“NLT (b)(4) % (Q) of in 30 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.

2.

(b)(4)

(b)(4) Please submit dissolution data [(N=12, individual, mean, CV%)] for the bio-batch and at least one batch of other strengths using this new dissolution method.

(b)(4)

(b)(4)

please submit the information/data showing the suitability/discriminating ability of the proposed dissolution method for your proposed drug product.

The Applicant responded to the above Biopharmaceutics Information Request (IR) on February 6, 2020 and accepted the recommended dissolution acceptance criteria of $Q=(b)(4)\%$ at 30 minutes for the 49 mg/51 mg and 97 mg/103 mg strengths. The Applicant also proposed the same dissolution acceptance criterion of $Q=(b)(4)\%$ at 30 minutes for their 24 mg/26 mg strength. The Applicant provided dissolution data using the new FDA dissolution database method, however, they proposed to continue using their originally proposed dissolution method. Given the available data, the response is acceptable.



Churg
Chan

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Om
Anand

Digitally signed by Om Anand
Date: 2/28/2020 10:00:25AM
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Marco A.
Bennett

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ANDA Executive Summary

1. Application/Product Information

ANDA Number.	213676
Review Cycle #	6
Applicant Name	Laurus Labs Limited
Drug Product Name	Sacubitril and Valsartan Tablets 24 mg/26 mg. 49 mg/51 mg and 97 mg/ 103 mg
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 sodium 194mg; Valsartan disodium 206 mg
Rx/OTC Dispensed	Rx
Proposed Indication	(b)(4)
Drug Product Description	24 mg/26 mg: Violet white color, oval shaped, biconvex film-coated tablets debossed with "S5" on one side and plain on the other side. 49 mg/51 mg: Pale yellow color, oval shaped, biconvex film-coated tablets debossed with "S1" on one side and plain on the other side. 97 mg/103 mg: Light pink color, oval shaped, biconvex film-coated tablets debossed with "S2" on one side and plain on the other side
Co-packaged product information	N/A

Device information, if any:	N/A		
Storage Temperature/ Conditions	20°C to 25°C		
Review Team	Discipline	Primary	Secondary
	<i>Drug Substance</i>	Xihong Wang/ Xianru Sun	Marco A. Bennett/ Erin Skoda
	<i>Drug Product/ Labeling</i>	Xihong Wang	Marco A. Bennett
	<i>Manufacturing</i>	Mirtha Millones / Md Abdullah Mahmud	Bo Jiang / Zhaoyang Meng
	<i>Biopharmaceutics</i>	Churg Chan	Om Anand
	<i>Microbiology</i>	N/A	N/A
	<i>Other (specify):</i>	N/A	N/A
	<i>RBPM</i>	Ify Mordi	
	<i>ATL</i>	Marco A. Bennett	
Consults	Discipline Consulted	Recommendation	Date
	N/A	N/A	N/A

2. Submission Document(s) Reviewed

Submission(s) Assessed	Documents Date	Disciplines Affected
Original/Initial Submission	07/08/2019	Quality
Quality/Response to Information Request	09/16/2019	Quality
Quality/Response to Discipline Review Letter	02/06/2020	Quality
Quality/Response to Information Request	03/02/2020	Quality

Resubmission/After Action- Complete	07/01/2020	Quality
Resubmission/After Action- Complete	05/03/2021	Quality
Amendment	08/02/2021	Quality
Resubmission/After Action- Complete	11/26/2021	DP
Resubmission/After Action- Complete	03/17/2022	DP, MFG
Gratuitous Amendment (Subject of Labeling review)	09/23/2022	Labeling
Gratuitous Amendment (Subject of review #6)	11/18/2022	DP
Resubmission/After Action- Complete	05/15/2023	DP
Quality/Response to Information Request	06/12/2023	Process

3. Related/Supporting Documents

a. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Assessor/ Comments
33647	II	Laurus Labs Limited	Sacubitril-Valsartan 3Na Complex	Inadequate	12/14/2023	Xianru Sun

b. Other Documents: *IND, RLD, RS, Approved ANDA*

Document	Application Number	Description
NDA (RLD)	NDA 207620	ENTRESTO® (sacubitril and valsartan) tablets 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg, manufactured by Novartis Pharmaceuticals Corporation. Approval date: 07/07/2015

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.*)

1. None

Drug Substance Deficiencies

1. None

Drug Product Deficiencies

1. None

Labeling Deficiencies *(Please contact OGD if you identify any Labeling deficiencies with your comments)*

1. None

Manufacturing Deficiencies

1. None

Biopharmaceutics Deficiencies

1. None

Microbiology Deficiencies

1. None

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. None

Additional Comments:

In addition to responding to the deficiencies presented above, please note and acknowledge the following comment(s) in your response: None

5. Basis for Recommendation

a. Summary of Rationale for Recommendation:

OPQ recommends approval of this ANDA on the basis that OLDP (CMC), Process, Microbiology and Facilities are all adequate a summary paragraph outlining reasons for OPQ action recommendation.

NDSRI Impacted Application: No
If yes, Risk Mitigated? NA

b. Recommendation by Subdiscipline:

Drug Substance: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view [Justification Statements](#))

1. N/A

Drug Product: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view [Justification Statements](#))

1. N/A

Quality Labeling: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view [Justification Statements](#))

1. N/A

Manufacturing: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view [Justification Statements](#))

1. N/A

Biopharmaceutics: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view [Justification Statements](#))

1. N/A

Microbiology: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view [Justification Statements](#))

1. N/A

Environmental: N/A

Provide justification(s) (for major deficiencies only):
(Click link to view [Justification Statements](#))

1. N/A

6. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments: None

Comparability Protocols (PACMP): No
Comments: None

Additional Comments: None



Marco A.
Bennett

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DRUG PRODUCT QUALITY ASSESSMENT

ANDA 213676 (Review Cycle # 06)

**Sacubitril and Valsartan Tablets,
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

Xihong Wang

Division of Immediate Release Products I/Branch II

Office of Lifecycle Drug Products

Office of Pharmaceutical Quality

DELETED PAGES INFORMATION SHEET

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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.

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ANDA 213676 (Assessment Cycle # 06)

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	Laurus Labs Limited Second Floor, Serene Chambers, Road No.7, Banjara Hills Hyderabad, Telangana India, 500034
Drug Product Manufacturer	(b) (4)
US agent, if applicable	☐ N/A ☒ (See Below) Sharath Koripally, Senior Director RA, QA & PV Laurus Generics Inc. 400 Connell Drive, Suite 5200 Berkeley Heights, NJ 07922 Tel: (718) 510-6822 Email: sharath.koripally@laurusgenerics.com
Proposed Indication	(b) (4)

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original (Subject of review #1)	07/08/2019	All
Amendment: Response to DRL-Labeling dated 10/25/19 (Subject of review #1)	11/07/2019	Labeling
Amendment: Response to DRL-Labeling dated 01/03/20 (Subject of review #1, IR#1)	02/06/2020	DP, Biopharm, Process
Amendment: Response to IR letter from the agency (Biopharm) dated 02/20/2020 (Subject of Biopharm review)	03/02/2020	Biopharm
Amendment: Response to CR letter from the agency dated 05/04/2020 (Subject of review #2)	07/01/2020	DP, Facility, BE
Amendment: Response to CR letter from the agency dated 02/22/2021 (Subject of review #3)	05/03/2021	DP, Labeling
General Correspondence: Change in US agent (Updated in the table above)	08/02/2021	
Amendment: Response to CR letter from the agency dated 10/04/2021 (Subject of Labeling review)	11/26/2021	Labeling
Amendment: Response to CR letter from the agency dated 02/23/2022 (Subject of review #5)	03/17/2022	DP, Labeling
Gratuitous Amendment (Subject of Labeling review)	09/23/2022	Labeling

Gratuitous Amendment (Subject of review #6)	11/18/2022	DP
Amendment: Response to CR-Major letter from the agency dated 12/10/2022 (Subject of review #6)	05/15/2023	DP
Amendment: Response to IR letter from the agency dated 06/08/2023 (Subject of process review)	06/12/2023	Process

QUALITY ASSESMENT DATA SHEET

[IQA ANDA Assessment Guide Reference](#)

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Reviewed	Comments
33647	II	Laurus Labs Limited	Sacubitril-Valsartan 3Na Complex	Adequate	12/14/2023	Xianru Sun
Other DMF: ☐ N/A ☒ (See Below)						
(b)(4)	III	(b)(4)	(b)(4)			
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	IV					

(b)(4)

B. OTHER DOCUMENTS: IND, RLD, RS, Approved ANDA

Document	Application Number	Brand Name	Description
NDA (RLD)	NDA 207620	ENTRESTO® (sacubitril and valsartan) tablets	ENTRESTO® (sacubitril and valsartan) tablets 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg, manufactured by Novartis Pharmaceuticals Corporation. Approval date: 07/07/2015

2. CONSULTS: None

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology				
CDRH-ODE				
CDRH-OC				
Clinical				
Other				

30 Pages have been withheld in full as b4 (CCI/TS) immediately following this page

CHAPTER I: DRUG SUBSTANCE

[IQA ANDA Assessment Guide Reference](#)

Drug Substance Name	Sacubitril-Valsartan 3Na Complex
DMF Number (If Applicable)	033647
DMF Status	Inadequate - Major
DMF Holder	Laurus Labs Limited

Overall Assessment Recommendation for DS:

DRL

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.

Highlight Key Issues from Last Cycle and Their Resolution:

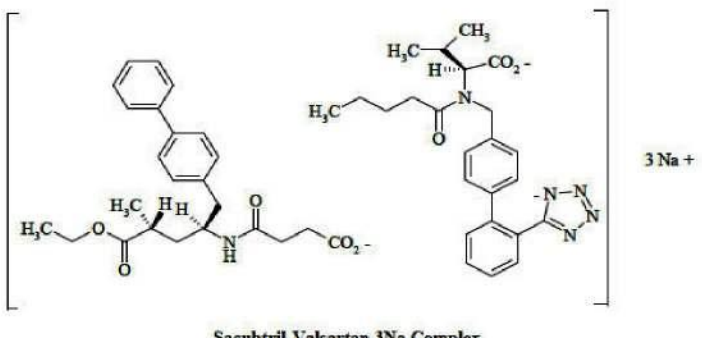
N/A - This is the review of original ANDA

Concise Description of Outstanding Issues:

Choose an item.

Select Number of Approved Comparability Protocols: 0

S.1 GENERAL INFORMATION

Nomenclature/Chemical name	: Tri sodium [3-((1 <i>S</i> ,3 <i>R</i>)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl -1-butylcarbamoyl)propionate-(<i>S</i>)-3'-methyl-2'-(pentanoyl {2''-(tetrazol-5-ylate) biphenyl-4'-ylmethyl} amino)butyrate]				
	(or) Tri sodium (4-[[[(1 <i>S</i> ,3 <i>R</i>)-1-([1,1'-biphenyl-4-ylmethyl-4-ethoxy-3-methyl-4-oxobutyl]amino)-4-oxobutanoate)(<i>N</i> -pentanoyl- <i>N</i> -{2'-(1 <i>H</i> -tetrazol-1-id-5-yl) [1,1'-biphenyl]-4-yl]methyl}- <i>L</i> -valinate)				
	<table border="1"> <thead> <tr> <th>Sacubitril</th> <th>Valsartan</th> </tr> </thead> <tbody> <tr> <td>4-[[[(1<i>S</i>,3<i>R</i>)-1-([1,1'-Biphenyl] -4-ylmethyl)-4-ethoxy -3-methyl-4-oxobutyl]amino]-4-oxobutanoic acid</td> <td><i>N</i>-Pentanoyl-<i>N</i>-{[2'-(1<i>H</i>-tetrazol-5-yl)[1,1'-biphenyl] -4-yl]methyl}-<i>L</i>-valine</td> </tr> </tbody> </table>	Sacubitril	Valsartan	4-[[[(1 <i>S</i> ,3 <i>R</i>)-1-([1,1'-Biphenyl] -4-ylmethyl)-4-ethoxy -3-methyl-4-oxobutyl]amino]-4-oxobutanoic acid	<i>N</i> -Pentanoyl- <i>N</i> -{[2'-(1 <i>H</i> -tetrazol-5-yl)[1,1'-biphenyl] -4-yl]methyl}- <i>L</i> -valine
Sacubitril	Valsartan				
4-[[[(1 <i>S</i> ,3 <i>R</i>)-1-([1,1'-Biphenyl] -4-ylmethyl)-4-ethoxy -3-methyl-4-oxobutyl]amino]-4-oxobutanoic acid	<i>N</i> -Pentanoyl- <i>N</i> -{[2'-(1 <i>H</i> -tetrazol-5-yl)[1,1'-biphenyl] -4-yl]methyl}- <i>L</i> -valine				
International Non-proprietary Name (INN)	: Not reported				
Compendial Name (WHO)	: Not reported				
United States Adopted Name (USAN)	: Sacubitril and valsartan				
Molecular Structure	: 				
Molecular Formula	: C ₄₈ H ₅₅ N ₆ O ₈ .3Na				
CAS number	: 936623-90-4				
Relative Molecular mass	: 912.95				
Pharmacological Class	: Angiotensin II receptor and neprilysin inhibitor for the treatment of chronic heart failure (NYHA Class II-IV) and reduced ejection fraction.				

Physical form	: White to off-white solid
(b)(4)	

Updates in review #3 as per AM dated 05/03/2021 are in light Blue
 Updates in review #6 as per AM dated 05/15/2023 are in dark red

Applicable ICH Identification and Qualification thresholds:

MDD		ICH Identification threshold	ICH Qualification threshold
Sacubitril sodium:	(b)(4)	0.10%	0.15%
Valsartan disodium:		0.10%	0.15%

Listing of related substances in DS:

14 Pages have been withheld in full as b4 (CCI/TS)
 immediately following this page

CHAPTER II: DRUG PRODUCT

[IQA ANDA Assessment Guide Reference](#)

Overall Assessment Recommendation: **Discipline Review Letter (DRL)**

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:

Drug Product CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Review Cycle #2	Comments*
Physical stability (solid state)	36 Medium	(b)(4)	Low	(b)(4)
Chemical Stability	48 Medium		Low	
Assay	18 Low		Low	
Content uniformity	24 Low			

		(b)(4)		(b)(4)
Microbial limits	9 Low		Low	
Dissolution	48 Medium			

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 the 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. Biopharm review is inadequate.*
- *Elemental impurity compliance with ICH Q3D – status: Adequate*
- *Number of Comparability protocols included: 0*

RLD versus Generic Product – NOT FOR FOIA

(b) (4)

* For repacking purpose only

P.1 DESCRIPTION AND COMPOSITION

Component/Composition of Sacubitril and Valsartan Tablets 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg

Ingredients	Compendial Reference	Pharmaceutical Function	24mg/26mg	49mg/51mg	97mg/103mg	%w/w
			(mg/ Tablet)			
(b)(4)						
Sacubitril-Valsartan 3Na Complex [^]	In-House	Active Ingredient (b)(4)	(b)(4)			
Low-substituted hydroxypropylcellulose (b)(4)	USP-NF					
Microcrystalline Cellulose (b)(4)	USP-NF					
Crospovidone (b)(4) (b)(4)	USP-NF					
Silicon dioxide (b)(4) (b)(4)	USP-NF					
Magnesium Stearate (b)(4) (b)(4)	USP-NF					

(b)(4)

Weight of Coated Tablet	103.000	206.000	412.000	100.000

(b)(4)

R REGIONAL INFORMATION

Environmental

- Laurus Labs Limited states that for this Abbreviated New Drug Application (ANDA) we are subject to a categorical exclusion from the requirement to prepare an Environmental Assessment Statement, as per 21 CFR § 25.30, 25.31, 25.33 and 25.15 (d).
- This ANDA is for the drug product which will not be indicated for administration at a higher dose level, nor for a longer duration, or for different indications than those that are in effect. No extraordinary circumstances, as outlined in 21 CFR § 25.21, exist. Hence, a categorical exclusion from the requirement to prepare an Environmental Assessment is hereby requested.
- Also, Laurus Labs Limited, hereby states that we are in compliance with all federal, state and local environmental laws.

Assessment:
Adequate

Adequate

Methods Validation or Verification Package

Assessment:

Adequate

Comparability Protocols

Assessment:
N/A

Choose an item.

Lifecycle Management Considerations

DRUG PRODUCT LIST OF DEFICIENCIES

1.

2.

3.

4.

(b) (4)

(b) (4)

CHAPTER III: ENVIRONMENTAL

[IQA ANDA Assessment Guide Reference](#)

R REGIONAL INFORMATION

Environmental

- Laurus Labs Limited states that for this Abbreviated New Drug Application (ANDA) we are subject to a categorical exclusion from the requirement to prepare an Environmental Assessment Statement, as per 21 CFR § 25.30, 25.31, 25.33 and 25.15 (d).
- This ANDA is for the drug product which will not be indicated for administration at a higher dose level, nor for a longer duration, or for different indications than those that are in effect. No extraordinary circumstances, as outlined in 21 CFR § 25.21, exist. Hence, a categorical exclusion from the requirement to prepare an Environmental Assessment is hereby requested.
- Also, Laurus Labs Limited, hereby states that we are in compliance with all federal, state and local environmental laws.

Assessment:
Adequate

Adequate

CHAPTER IV: LABELING

[IQA ANDA Assessment Guide Reference](#)

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	Dimension (mm) (Length x Width)	Imprint Code
24mg/26mg	9.11x 5.08	Violet white color, oval, biconvex film-coated tablets debossed with "S5" on one side and plain on the other side.
49mg/51mg	12.75 x 5.90	Pale yellow color, oval, biconvex film-coated tablets debossed with "S1" on one side and plain on the other side.
97mg/103mg	12.57 x 6.85	Light pink color, oval, biconvex film-coated tablets debossed with "S2" on one side and plain on the other side.

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

A. Drug Substance Deficiencies

None

B. Drug Product Deficiencies

None

C. Labeling Deficiencies

None

(END OF DRUG PRODUCT QUALITY ASSESSMENT)

Signature Block:

Primary DP Assessor: *Xihong Wang*

Date: 12/19/19;
3/31/2020;
1/22/2021
7/1/2021,
09/16/2021;
01/27/2022,
02/04/2022;
11/08/2022,
12/07/2022;
12/06/2023,
12/14/2023

Secondary DP Assessor: *Marco Bennett*

Date: 12/19/2019;
04.01.2020;
04.14.2020;
01.22.2021;
07.02.2021;
09.17.2021;
01.31.2022;
02.04.2022;
12.08.2022;
12.14.2023



Xihong
Wang

Digitally signed by Xihong Wang
Date: 12/14/2023 03:40:59PM
GUID: 508da7410002ba99af7b0597dc38d164



Marco A.
Bennett

Digitally signed by Marco A. Bennett
Date: 12/14/2023 04:57:20PM
GUID: 508da705000289bae41af5c5413d8455



**U.S. FOOD & DRUG
ADMINISTRATION**

DRUG PRODUCT QUALITY ASSESSMENT

ANDA 213676 (Review Cycle # 05)

Sacubitril and Valsartan Tablets,

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

Xihong Wang

Division of Immediate Release Products I/Branch II

Office of Lifecycle Drug Products

Office of Pharmaceutical Quality

Justification for CR-Major:

The drug product deficiencies have been classified as MAJOR as noted in the Guidance for Industry, ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018) because the firm may need to develop a new analytical method for nitrosamine impurity in DP or the firm should validate the FDA's method and provide data to demonstrate that the in-house method is equivalent to the FDA's method. Upon receipt, in FDA's judgement, the review of this information will require thorough evaluation and potentially affects other aspects of the application and the related conclusions

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ANDA 213676 (Assessment Cycle # 05)

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	Laurus Labs Limited Second Floor, Serene Chambers, Road No.7, Banjara Hills Hyderabad, Telangana India, 500034
Drug Product Manufacturer	(b) (4)
US agent, if applicable	☐ N/A ☒ (See Below) Sharath Koripally, Senior Director RA, QA & PV Laurus Generics Inc. 400 Connell Drive, Suite 5200 Berkeley Heights, NJ 07922 Tel: (718) 510-6822 Email: sharath.koripally@laurusgenerics.com
Proposed Indication	(b) (4)

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original (Subject of review #1)	07/08/2019	All
Amendment: Response to DRL-Labeling dated 10/25/19 (Subject of review #1)	11/07/2019	Labeling
Amendment: Response to DRL-Labeling dated 01/03/20 (Subject of review #1, IR#1)	02/06/2020	DP, Biopharm, Process
Amendment: Response to IR letter from the agency (Biopharm) dated 02/20/2020 (Subject of Biopharm review)	03/02/2020	Biopharm
Amendment: Response to CR letter from the agency dated 05/04/2020 (Subject of review #2)	07/01/2020	DP, Facility, BE
Amendment: Response to CR letter from the agency dated 02/22/2021 (Subject of review #3)	05/03/2021	DP, Labeling
General Correspondence: Change in US agent (Updated in the table above)	08/02/2021	
Amendment: Response to CR letter from the agency dated 10/04/2021 (Subject of Labeling review)	11/26/2021	Labeling
Amendment: Response to CR letter from the agency dated 02/23/2022 (Subject of review #5)	03/17/2022	DP, Labeling
Gratuitous Amendment (Subject of Labeling review)	09/23/2022	Labeling

QUALITY ASSESMENT DATA SHEET

[IQA ANDA Assessment Guide Reference](#)

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Reviewed	Comments
33647	II	Laurus Labs Limited	Sacubitril-Valsartan 3Na Complex	Inadequate	12/07/2022	Xianru Sun
Other DMF: ☐ N/A ☒ (See Below)						
(b)(4)	III	(b)(4)	(b)(4)			
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	IV					

(b)(4)

B. OTHER DOCUMENTS: IND, RLD, RS, Approved ANDA

Document	Application Number	Brand Name	Description
NDA (RLD)	NDA 207620	ENTRESTO® (sacubitril and valsartan) tablets	ENTRESTO® (sacubitril and valsartan) tablets 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg, manufactured by Novartis Pharmaceuticals Corporation. Approval date: 07/07/2015

2. CONSULTS: None

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology				
CDRH-ODE				
CDRH-OC				
Clinical				
Other				

26 Pages have been withheld in full as b4 (CCI/TS) immediately following this page

CHAPTER I: DRUG SUBSTANCE

[IQA ANDA Assessment Guide Reference](#)

Drug Substance Name	Sacubitril-Valsartan 3Na Complex
DMF Number (If Applicable)	033647
DMF Status	Inadequate - Major
DMF Holder	Laurus Labs Limited

Overall Assessment Recommendation for DS:

DRL

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.

Highlight Key Issues from Last Cycle and Their Resolution:

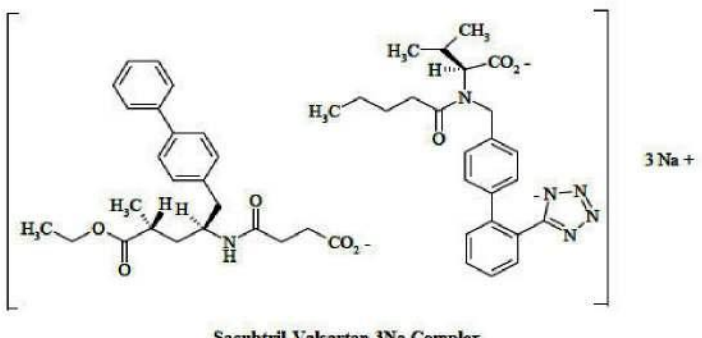
N/A - This is the review of original ANDA

Concise Description of Outstanding Issues:

Choose an item.

Select Number of Approved Comparability Protocols: 0

S.1 GENERAL INFORMATION

Nomenclature/Chemical name	: Tri sodium [3-((1 <i>S</i> ,3 <i>R</i>)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl -1-butylcarbamoyl)propionate-(<i>S</i>)-3'-methyl-2'-(pentanoyl {2''-(tetrazol-5-ylate) biphenyl-4'-ylmethyl} amino)butyrate]				
	(or) Tri sodium (4-[[[(1 <i>S</i> ,3 <i>R</i>)-1-([1,1'-biphenyl-4-ylmethyl-4-ethoxy-3-methyl-4-oxobutyl]amino)-4-oxobutanoate)(<i>N</i> -pentanoyl- <i>N</i> -{2'-(1 <i>H</i> -tetrazol-1-id-5-yl) [1,1'-biphenyl]-4-yl]methyl}- <i>L</i> -valinate)				
	<table border="1"> <thead> <tr> <th>Sacubitril</th> <th>Valsartan</th> </tr> </thead> <tbody> <tr> <td>4-[[[(1<i>S</i>,3<i>R</i>)-1-([1,1'-Biphenyl] -4-ylmethyl)-4-ethoxy -3-methyl-4-oxobutyl]amino]-4-oxobutanoic acid</td> <td><i>N</i>-Pentanoyl-<i>N</i>-{[2'-(1<i>H</i>-tetrazol-5-yl)[1,1'-biphenyl] -4-yl]methyl}-<i>L</i>-valine</td> </tr> </tbody> </table>	Sacubitril	Valsartan	4-[[[(1 <i>S</i> ,3 <i>R</i>)-1-([1,1'-Biphenyl] -4-ylmethyl)-4-ethoxy -3-methyl-4-oxobutyl]amino]-4-oxobutanoic acid	<i>N</i> -Pentanoyl- <i>N</i> -{[2'-(1 <i>H</i> -tetrazol-5-yl)[1,1'-biphenyl] -4-yl]methyl}- <i>L</i> -valine
Sacubitril	Valsartan				
4-[[[(1 <i>S</i> ,3 <i>R</i>)-1-([1,1'-Biphenyl] -4-ylmethyl)-4-ethoxy -3-methyl-4-oxobutyl]amino]-4-oxobutanoic acid	<i>N</i> -Pentanoyl- <i>N</i> -{[2'-(1 <i>H</i> -tetrazol-5-yl)[1,1'-biphenyl] -4-yl]methyl}- <i>L</i> -valine				
International Non-proprietary Name (INN)	: Not reported				
Compendial Name (WHO)	: Not reported				
United States Adopted Name (USAN)	: Sacubitril and valsartan				
Molecular Structure	:  Sacubitril-Valsartan 3Na Complex				
Molecular Formula	: C ₄₈ H ₅₅ N ₆ O ₈ .3Na				
CAS number	: 936623-90-4				
Relative Molecular mass	: 912.95				
Pharmacological Class	: Angiotensin II receptor and neprilysin inhibitor for the treatment of chronic heart failure (NYHA Class II-IV) and reduced ejection fraction.				

Physical form	: White to off-white solid
	(b)(4)

CHAPTER II: DRUG PRODUCT

[IQA ANDA Assessment Guide Reference](#)

Overall Assessment Recommendation: **Discipline Review Letter (DRL)**

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:

Drug Product CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Review Cycle #2	Comments*
Physical stability (solid state)	36 Medium	(b)(4)	Low	(b)(4)
Chemical Stability	48 Medium		Low	
Assay	18 Low		Low	
Content uniformity	24 Low			

		(b)(4)		(b)(4)
Microbial limits	9 Low		Low	
Dissolution	48 Medium			

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 the 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. Biopharm review is inadequate.*
- *Elemental impurity compliance with ICH Q3D – status: Adequate*
- *Number of Comparability protocols included: 0*

RLD versus Generic Product – NOT FOR FOIA

(b) (4)

* For repacking purpose only

P.1 DESCRIPTION AND COMPOSITION

Component/Composition of Sacubitril and Valsartan Tablets 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg

Ingredients	Compendial Reference	Pharmaceutical Function	24mg/26mg	49mg/51mg	97mg/103mg	%w/w
			(mg/ Tablet)			
(b)(4)						
Sacubitril-Valsartan 3Na Complex [^]	In-House	Active Ingredient	(b)(4)			
Low-substituted hydroxypropylcellulose (b)(4)	USP-NF	(b)(4)				
Microcrystalline Cellulose (b)(4)	USP-NF					
Crospovidone (b)(4)	USP-NF					
Silicon dioxide (b)(4)	USP-NF					
Magnesium Stearate (b)(4)	USP-NF					
(b)(4)						
Weight of Coated Tablet			103.000	206.000	412.000	100.000

(b)(4)

R REGIONAL INFORMATION

Environmental

- Laurus Labs Limited states that for this Abbreviated New Drug Application (ANDA) we are subject to a categorical exclusion from the requirement to prepare an Environmental Assessment Statement, as per 21 CFR § 25.30, 25.31, 25.33 and 25.15 (d).
- This ANDA is for the drug product which will not be indicated for administration at a higher dose level, nor for a longer duration, or for different indications than those that are in effect. No extraordinary circumstances, as outlined in 21 CFR § 25.21, exist. Hence, a categorical exclusion from the requirement to prepare an Environmental Assessment is hereby requested.
- Also, Laurus Labs Limited, hereby states that we are in compliance with all federal, state and local environmental laws.

Assessment:
Adequate

Adequate

Methods Validation or Verification Package

Assessment:

Adequate

Comparability Protocols

Assessment:
N/A

Choose an item.

Lifecycle Management Considerations

DRUG PRODUCT LIST OF DEFICIENCIES

1.

2.

3.

4.

(b) (4)

(b) (4)

5.

6.

7.

(b) (4)

CHAPTER III: ENVIRONMENTAL

[IQA ANDA Assessment Guide Reference](#)

R REGIONAL INFORMATION

Environmental

- Laurus Labs Limited states that for this Abbreviated New Drug Application (ANDA) we are subject to a categorical exclusion from the requirement to prepare an Environmental Assessment Statement, as per 21 CFR § 25.30, 25.31, 25.33 and 25.15 (d).
- This ANDA is for the drug product which will not be indicated for administration at a higher dose level, nor for a longer duration, or for different indications than those that are in effect. No extraordinary circumstances, as outlined in 21 CFR § 25.21, exist. Hence, a categorical exclusion from the requirement to prepare an Environmental Assessment is hereby requested.
- Also, Laurus Labs Limited, hereby states that we are in compliance with all federal, state and local environmental laws.

Assessment:
Adequate

Adequate

CHAPTER IV: LABELING

[IQA ANDA Assessment Guide Reference](#)

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	Dimension (mm) (Length x Width)	Imprint Code
24mg/26mg	9.11x 5.08	Violet white color, oval, biconvex film-coated tablets debossed with "S5" on one side and plain on the other side.
49mg/51mg	12.75 x 5.90	Pale yellow color, oval, biconvex film-coated tablets debossed with "S1" on one side and plain on the other side.
97mg/103mg	12.57 x 6.85	Light pink color, oval, biconvex film-coated tablets debossed with "S2" on one side and plain on the other side.

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

A. Drug Substance Deficiencies

1. (b) (4)
2. (b) (4)

B. Drug Product Deficiencies

1. (b) (4)

C. Labeling Deficiencies

None

(END OF DRUG PRODUCT QUALITY ASSESSMENT)

Signature Block:

Primary DP Assessor: Xihong Wang

Date: 12/19/19;
3/31/2020;

Secondary DP Assessor: _____ *Date:* _____
Marco Bennett _____
1/22/2021
7/1/2021,
09/16/2021;
01/27/2022,
02/04/2022;
11/08/2022,
12/07/2022
12/19/2019;
04.01.2020;
04.14.2020;
01.22.2021;
07.02.2021;
09.17.2021;
01.31.2022;
02.04.2022;
12.08.2022



Xihong
Wang

Digitally signed by Xihong Wang
Date: 12/08/2022 07:59:11AM
GUID: 508da7410002ba99af7b0597dc38d164



Marco A.
Bennett

Digitally signed by Marco A. Bennett
Date: 12/08/2022 11:00:26AM
GUID: 508da705000289bae41af5c5413d8455

ANDA Executive Summary

1. Application/Product Information

ANDA Number.	213676		
Review Cycle #	5		
Applicant Name	Laurus Labs Limited		
Drug Product Name	Sacubitril and Valsartan Tablets 24 mg/26 mg. 49 mg/5 l mg and 97 mg/ l 03 mg		
Dosage Form. (click (+) for more than one)	Tablet		
Proposed Strength(s)	24 mg/26 mg. 49 mg/5 l mg and 97 mg/ l 03 mg		
Route of Administration (click (+) for more than one)	Oral		
Maximum Daily Dose	Sacubitril sodium 194mg; Valsartan disodium 206 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	(b)(4)		
Drug Product Description	White to off-white solid		
Co-packaged product information	N/A		
Device information, if any:	N/A		
Storage Temperature/ Conditions	20°C to 25°C		
Review Team	Discipline	Primary	Secondary
	<i>Drug Substance</i>	Xianru Sun	Erin Skoda

	<i>Drug Product/ Labeling</i>	Xihong Wang	Marco A. Bennett
	<i>Manufacturing</i>	Md Abdullah Mahmud	Zhaoyang Meng
	<i>Biopharmaceutics</i>	N/A	N/A
	<i>Microbiology</i>	N/A	N/A
	<i>Other (specify):</i>	N/A	N/A
	<i>RBPM</i>	Helina Zenebe	
	<i>ATL</i>	Marco A. Bennett	
Consults	Discipline Consulted	Recommendation	Date
	N/A		

2. Submission Document(s) Reviewed

Submission(s) Assessed	Documents Date	Disciplines Affected
Original/Initial Submission	07/08/2019	Quality
Quality/Response to Information Request	09/16/2019	Quality
Quality/Response to Discipline Review Letter	02/06/2020	Quality
Quality/Response to Information Request	03/02/2020	Quality
Resubmission/After Action- Complete	07/1/2020	Quality
Resubmission/After Action- Complete	05/03/2021	Quality
Resubmission/After Action- Complete	11/26/2021	DP
Resubmission/After Action- Complete	03/17/2022	DP, MFG

3. Related/Supporting Documents

a. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Assessor/Comments
33647	II	Laurus Labs Limited	Sacubitril-Valsartan 3Na Complex	Inadequate	12/07/2022	Xianru Sun

b. Other Documents: *IND, RLD, RS, Approved ANDA*

Document	Application Number	Description
NDA (RLD)	NDA 207620	ENTRESTO® (sacubitril and valsartan) tablets 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg, manufactured by Novartis Pharmaceuticals Corporation. Approval date: 07/07/2015

4. Final Overall recommendation – Complete Response-Major

Deficiencies (if applicable):

Overall Quality Deficiencies - Optional (*Deficiencies that affect multiple sub-disciplines; for subheadings use the format shown, for all deficiencies.*): **None**

Drug Substance Deficiencies –

1.

(b) (4)

2.

Drug Product Deficiencies –

1.

(b) (4)

Labeling Deficiencies (*Please contact OGD if you identify any Labeling deficiencies with your comments*): **None**

Manufacturing Deficiencies

a. **Process:** - None

b. **Facility:** - None

Biopharmaceutics Deficiencies: - None

Microbiology Deficiencies: - None

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*):
None

Additional Comments:

In addition to responding to the deficiencies presented above, please note and acknowledge the following comment(s) in your response: N/A

5. Basis for Recommendation

a. Summary of Rationale for Recommendation:

OPQ recommends CR-Major for this ANDA on the basis that OLDP (CMC) is a Major since analytical method for nitrosamine impurity is missing.

b. Recommendation by Subdiscipline:

Drug Substance: INADEQUATE-MINOR

Provide justification(s) (for major deficiencies only):

(Click link to view [Justification Statements](#))

1. None

Drug Product: INADEQUATE-MAJOR

Provide justification(s) (for major deficiencies only):

(Click link to view [Justification Statements](#))

The drug product deficiencies have been classified as MAJOR as noted in Appendix A Section A, 2i in the Guidance for Industry, ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018) because the firm may need to develop a new analytical method for nitrosamine impurity in DP or the firm should validate the FDA's method and provide data to demonstrate that the in-house method is equivalent to the FDA's method. Upon receipt, in FDA's judgement, the review of this information will require thorough evaluation and potentially affects other aspects of the application and the related conclusions.

Quality Labeling: ADEQUATE

Provide justification(s) (for major deficiencies only):

(Click link to view [Justification Statements](#))

1. None

Manufacturing: ADEQUATE

Provide justification(s) (for major deficiencies only):

(Click link to view [Justification Statements](#))

1. None

Biopharmaceutics: ADEQUATE

Provide justification(s) (for major deficiencies only):

(Click link to view [Justification Statements](#))

1. None

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: N/A



Marco A.
Bennett

Digitally signed by Marco A. Bennett

Date: 12/08/2022 09:51:16AM

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ANDA Executive Summary

1. Application/Product Information

ANDA Number.	213676		
Review Cycle #	5		
Applicant Name	Laurus Labs Limited		
Drug Product Name	Sacubitril and Valsartan Tablets 24 mg/26 mg. 49 mg/5 l mg and 97 mg/ l 03 mg		
Dosage Form. (click (+) for more than one)	Tablet		
Proposed Strength(s)	24 mg/26 mg. 49 mg/5 l mg and 97 mg/ l 03 mg		
Route of Administration (click (+) for more than one)	Oral		
Maximum Daily Dose	Sacubril sodium 194mg; Valsartan disodium 206 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	(b) (4)		
Drug Product Description	White to off-white solid		
Co-packaged product information	N/A		
Device information, if any:	N/A		
Storage Temperature/ Conditions	20°C to 25°C		
Review Team	Discipline	Primary	Secondary
	<i>Drug Substance</i>	Xianru Sun	Erin Skoda

	<i>Drug Product/ Labeling</i>	Xihong Wang	Marco A. Bennett
	<i>Manufacturing</i>	Md Abdullah Mahmud	Zhaoyang Meng
	<i>Biopharmaceutics</i>	N/A	N/A
	<i>Microbiology</i>	N/A	N/A
	<i>Other (specify):</i>	N/A	N/A
	<i>RBPM</i>	Helina Zenebe	
	<i>ATL</i>	Marco A. Bennett	
Consults	Discipline Consulted	Recommendation	Date
	N/A		

2. Submission Document(s) Reviewed

Submission(s) Assessed	Documents Date	Disciplines Affected
Original/Initial Submission	07/08/2019	Quality
Quality/Response to Information Request	09/16/2019	Quality
Quality/Response to Discipline Review Letter	02/06/2020	Quality
Quality/Response to Information Request	03/02/2020	Quality
Resubmission/After Action- Complete	07/1/2020	Quality
Resubmission/After Action- Complete	05/03/2021	Quality
Resubmission/After Action- Complete	11/26/2021	DP
Resubmission/After Action- Complete	03/17/2022	DP, MFG

3. Related/Supporting Documents

a. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Assessor/ Comments
33647	II	Laurus Labs Limited	Sacubitril-Valsartan 3Na Complex	Adequate	10/07/2022	Xianru Sun

b. Other Documents: *IND, RLD, RS, Approved ANDA*

Document	Application Number	Description
NDA (RLD)	NDA 207620	ENTRESTO® (sacubitril and valsartan) tablets 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg, manufactured by Novartis Pharmaceuticals Corporation. Approval date: 07/07/2015

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.*): **None**

Drug Substance Deficiencies – None

Drug Product Deficiencies – None

Labeling Deficiencies (*Please contact OGD if you identify any Labeling deficiencies with your comments*): **None**

Manufacturing Deficiencies

a. **Process: - None**

b. **Facility: - None**

Biopharmaceutics Deficiencies: - None

Microbiology Deficiencies: - None

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**):
None

Additional Comments:

In addition to responding to the deficiencies presented above, please note and acknowledge the following comment(s) in your response: N/A

5. Basis for Recommendation

a. Summary of Rationale for Recommendation:

OPQ recommends approval of this ANDA on the basis that OLDP (CMC), Process, Biopharmaceutics and Facilities are all adequate a summary paragraph outlining reasons for OPQ action recommendation.

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: N/A



Marco A.
Bennett

Digitally signed by Marco A. Bennett

Date: 11/18/2022 10:58:28AM

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**U.S. FOOD & DRUG
ADMINISTRATION**

DRUG PRODUCT QUALITY ASSESSMENT

ANDA 213676 (Review Cycle # 05)

Sacubitril and Valsartan Tablets,

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

Xihong Wang

Division of Immediate Release Products I/Branch II

Office of Lifecycle Drug Products

Office of Pharmaceutical Quality

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ANDA 213676 (Assessment Cycle # 05)

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	Laurus Labs Limited Second Floor, Serene Chambers, Road No.7, Banjara Hills Hyderabad, Telangana India, 500034
Drug Product Manufacturer	(b) (4)
US agent, if applicable	☐ N/A ☒ (See Below) Sharath Koripally, Senior Director RA, QA & PV Laurus Generics Inc. 400 Connell Drive, Suite 5200 Berkeley Heights, NJ 07922 Tel: (718) 510-6822 Email: sharath.koripally@laurusgenerics.com
Proposed Indication	(b)(4)

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original (Subject of review #1)	07/08/2019	All
Amendment: Response to DRL-Labeling dated 10/25/19 (Subject of review #1)	11/07/2019	Labeling
Amendment: Response to DRL-Labeling dated 01/03/20 (Subject of review #1, IR#1)	02/06/2020	DP, Biopharm, Process
Amendment: Response to IR letter from the agency (Biopharm) dated 02/20/2020 (Subject of Biopharm review)	03/02/2020	Biopharm
Amendment: Response to CR letter from the agency dated 05/04/2020 (Subject of review #2)	07/01/2020	DP, Facility, BE
Amendment: Response to CR letter from the agency dated 02/22/2021 (Subject of review #3)	05/03/2021	DP, Labeling
General Correspondence: Change in US agent (Updated in the table above)	08/02/2021	
Amendment: Response to CR letter from the agency dated 10/04/2021 (Subject of Labeling review)	11/26/2021	Labeling
Amendment: Response to CR letter from the agency dated 02/23/2022 (Subject of review #5)	03/17/2022	DP, Labeling
Gratuitous Amendment (Subject of Labeling review)	09/23/2022	Labeling

QUALITY ASSESMENT DATA SHEET

[IQA ANDA Assessment Guide Reference](#)

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Reviewed	Comments
33647	II	Laurus Labs Limited	Sacubitril-Valsartan 3Na Complex	Adequate	10/07/2022	Xianru Sun
Other DMF: ☐ N/A ☒ (See Below)						
(b)(4)	III	(b)(4)	(b)(4)			
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	IV					

			(b)(4)		

B. OTHER DOCUMENTS: IND, RLD, RS, Approved ANDA

Document	Application Number	Brand Name	Description
NDA (RLD)	NDA 207620	ENTRESTO® (sacubitril and valsartan) tablets	ENTRESTO® (sacubitril and valsartan) tablets 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg, manufactured by Novartis Pharmaceuticals Corporation. Approval date: 07/07/2015

2. CONSULTS: None

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology				
CDRH-ODE				
CDRH-OC				
Clinical				
Other				

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.

CHAPTER I: DRUG SUBSTANCE

[IQA ANDA Assessment Guide Reference](#)

Drug Substance Name	Sacubitril-Valsartan 3Na Complex
DMF Number (If Applicable)	033647
DMF Status	Inadequate - Major
DMF Holder	Laurus Labs Limited

Overall Assessment Recommendation for DS:

DRL

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.

Highlight Key Issues from Last Cycle and Their Resolution:

N/A - This is the review of original ANDA

Concise Description of Outstanding Issues:

Choose an item.

Select Number of Approved Comparability Protocols: 0

S.1 GENERAL INFORMATION

Nomenclature/Chemical name	: Tri sodium [3-((1 <i>S</i> ,3 <i>R</i>)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl -1-butylcarbamoyl)propionate-(<i>S</i>)-3'-methyl-2'-(pentanoyl {2''-(tetrazol-5-ylate) biphenyl-4'-ylmethyl} amino)butyrate]				
	(or) Tri sodium (4-[[[(1 <i>S</i> ,3 <i>R</i>)-1-([1,1'-biphenyl-4-ylmethyl-4-ethoxy-3-methyl-4-oxobutyl]amino)-4-oxobutanoate)(N-pentanoyl-N-{2'-(1 <i>H</i> -tetrazol-1-id-5-yl) [1,1'-biphenyl]-4-yl]methyl}-L-valinate)				
	<table border="1"> <thead> <tr> <th>Sacubitril</th> <th>Valsartan</th> </tr> </thead> <tbody> <tr> <td>4-[[[(1<i>S</i>,3<i>R</i>)-1-([1,1'-Biphenyl] -4-ylmethyl)-4-ethoxy -3-methyl-4-oxobutyl]amino]-4-oxobutanoic acid</td> <td>N-Pentanoyl-N-{[2'-(1<i>H</i>-tetrazol-5-yl)[1,1'-biphenyl] -4-yl]methyl}-L-valine</td> </tr> </tbody> </table>	Sacubitril	Valsartan	4-[[[(1 <i>S</i> ,3 <i>R</i>)-1-([1,1'-Biphenyl] -4-ylmethyl)-4-ethoxy -3-methyl-4-oxobutyl]amino]-4-oxobutanoic acid	N-Pentanoyl-N-{[2'-(1 <i>H</i> -tetrazol-5-yl)[1,1'-biphenyl] -4-yl]methyl}-L-valine
Sacubitril	Valsartan				
4-[[[(1 <i>S</i> ,3 <i>R</i>)-1-([1,1'-Biphenyl] -4-ylmethyl)-4-ethoxy -3-methyl-4-oxobutyl]amino]-4-oxobutanoic acid	N-Pentanoyl-N-{[2'-(1 <i>H</i> -tetrazol-5-yl)[1,1'-biphenyl] -4-yl]methyl}-L-valine				
International Non-proprietary Name (INN)	: Not reported				
Compendial Name (WHO)	: Not reported				
United States Adopted Name (USAN)	: Sacubitril and valsartan				
Molecular Structure	: Sacubitril-Valsartan 3Na Complex				
Molecular Formula	: C ₄₈ H ₅₅ N ₆ O ₈ .3Na				
CAS number	: 936623-90-4				
Relative Molecular mass	: 912.95				
Pharmacological Class	: Angiotensin II receptor and neprilysin inhibitor for the treatment of chronic heart failure (NYHA Class II-IV) and reduced ejection fraction.				

Physical form	: White to off-white solid
	(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)

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CHAPTER II: DRUG PRODUCT

[IQA ANDA Assessment Guide Reference](#)

Overall Assessment Recommendation: Discipline Review Letter (DRL)

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:

Drug Product CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Review Cycle #2	Comments*
Physical stability (solid state)	36 Medium	(b)(4)	Low	(b)(4)
Chemical Stability	48 Medium		Low	
Assay	18 Low		Low	
Content uniformity	24 Low			

		(b)(4)		(b)(4)
Microbial limits	9 Low		Low	
Dissolution	48 Medium			

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 the 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. Biopharm review is inadequate.*
- *Elemental impurity compliance with ICH Q3D – status: Adequate*
- *Number of Comparability protocols included: 0*

RLD versus Generic Product – NOT FOR FOIA

(b) (4)

* For repacking purpose only

P.1 DESCRIPTION AND COMPOSITION

Component/Composition of Sacubitril and Valsartan Tablets 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg

Ingredients	Compendial Reference	Pharmaceutical Function	24mg/ 26mg	49mg/ 51mg	97mg/ 103mg	%w/w
			(mg/ Tablet)			
Intra-granular materials						
Sacubitril-Valsartan 3Na Complex [^]	In-House	Active Ingredient	(b)(4)			
Low-substituted hydroxypropylcellulose (b)(4)	USP-NF	(b)(4)				
Microcrystalline Cellulose (b)(4)	USP-NF					
Crospovidone (b)(4)	USP-NF					
Silicon dioxide (b)(4)	USP-NF					
Magnesium Stearate (b)(4)	USP-NF					
(b)(4)						
Weight of Coated Tablet			103.000	206.000	412.000	100.000

(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)

Assessment:

Inadequate

(b)(4)

R REGIONAL INFORMATION

Environmental

- Laurus Labs Limited states that for this Abbreviated New Drug Application (ANDA) we are subject to a categorical exclusion from the requirement to prepare an Environmental Assessment Statement, as per 21 CFR § 25.30, 25.31, 25.33 and 25.15 (d).
- This ANDA is for the drug product which will not be indicated for administration at a higher dose level, nor for a longer duration, or for different indications than those that are in effect. No extraordinary circumstances, as outlined in 21 CFR § 25.21, exist. Hence, a categorical exclusion from the requirement to prepare an Environmental Assessment is hereby requested.
- Also, Laurus Labs Limited, hereby states that we are in compliance with all federal, state and local environmental laws.

Assessment:

Adequate

Adequate

Methods Validation or Verification Package

Assessment:

Adequate

Comparability Protocols

Assessment:

Choose an item.

N/A

Lifecycle Management Considerations

DRUG PRODUCT LIST OF DEFICIENCIES

1.

2.

3.

4.

(b) (4)

(b) (4)

5.

6.

7.

(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.

CHAPTER III: ENVIRONMENTAL

[IQA ANDA Assessment Guide Reference](#)

R REGIONAL INFORMATION

Environmental

- Laurus Labs Limited states that for this Abbreviated New Drug Application (ANDA) we are subject to a categorical exclusion from the requirement to prepare an Environmental Assessment Statement, as per 21 CFR § 25.30, 25.31, 25.33 and 25.15 (d).
- This ANDA is for the drug product which will not be indicated for administration at a higher dose level, nor for a longer duration, or for different indications than those that are in effect. No extraordinary circumstances, as outlined in 21 CFR § 25.21, exist. Hence, a categorical exclusion from the requirement to prepare an Environmental Assessment is hereby requested.
- Also, Laurus Labs Limited, hereby states that we are in compliance with all federal, state and local environmental laws.

Assessment:
Adequate

Adequate

CHAPTER IV: LABELING

[IQA ANDA Assessment Guide Reference](#)

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	Dimension (mm) (Length x Width)	Imprint Code
24mg/26mg	9.11x 5.08	Violet white color, oval, biconvex film-coated tablets debossed with “S5” on one side and plain on the other side.
49mg/51mg	12.75 x 5.90	Pale yellow color, oval, biconvex film-coated tablets debossed with “S1” on one side and plain on the other side.
97mg/103mg	12.57 x 6.85	Light pink color, oval, biconvex film-coated tablets debossed with “S2” on one side and plain on the other side.

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

A. Drug Substance Deficiencies

None

B. Drug Product Deficiencies

None

C. Labeling Deficiencies

None

(END OF DRUG PRODUCT QUALITY ASSESSMENT)

Signature Block:

Primary DP Assessor: *Xihong Wang*

Date: 12/19/19;
3/31/2020;
1/22/2021
7/1/2021,
09/16/2021;
01/27/2022,
02/04/2022;
11/08/2022

Secondary DP Assessor: *Marco Bennett*

Date: 12/19/2019;
04.01.2020;
04.14.2020;
01.22.2021;
07.02.2021;
09.17.2021;
01.31.2022;
02.04.2022;
11.09.2022



Xihong
Wang

Digitally signed by Xihong Wang
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GUID: 508da7410002ba99af7b0597dc38d164



Marco A.
Bennett

Digitally signed by Marco A. Bennett
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MANUFACTURING INTEGRATED ASSESSMENT

Application ID	ANDA 213676
Drug Product Name	Sacubitril and Valsartan Tablets
Strengths	24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg
Dosage Form	Tablets
Administration Route	Oral
Indication	(b)(4)
Applicant Name	Laurus Labs Limited
RLD Number	207620

Note: Updates in this review cycle (R05, Amend-16) is typed in purple text.

Both Process and Facilities remain Adequate as assessed in previous cycle (A 213676-ORIG-AMEND-12).

(b)(4)

(b)(4). All facilities are found Adequate. The Overall Manufacturing Inspection Recommendation is Approve.

The latest Manufacturing Integrated Assessment (ANDA 213676-ORIG-1-AMEND-09, added on Dec 28, 2020) was not archived in Panorama. Therefore, the IQA document is uploaded in current review cycle for archival purpose only.

I. Manufacturing Summary

Facility Assessment Recommendation: Adequate

Process Assessment Recommendation: Adequate

Assessment Summary:

Sacubitril and Valsartan Tablets 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg is manufactured using (b)(4)

(b)(4)

List Submissions being assessed (Table):

Document Description (SD #)	Date Received

Original (SD# 0001)	07/08/2019
Response to IR (SD# 0003)	09/16/2019
Response to IR (SD#0007)	02/06/2020
Response to IR (SD#0008)	03/02/2020
Response to CR (SD#0009)	07/01/2020
Response to CR (SD #16)	03/17/2022

Highlight Key Issues from Last Cycle and Their Resolution: None

Concise Description of Outstanding Issues (List bullet points with key information and update as needed): None

Highlight Key Issues from Last Cycle and Their Resolution: 1st Cycle

Review #1

(b)(4)

Review #2

(b)(4)

Concise Description of Outstanding Issues (List bullet points with key information and update as needed):

- None

List Number of Comparability Protocols: None

1. Lifecycle Management Considerations

Post-approval inspection?	No
Lifecycle considerations	No
Choose an item.	

2. Facilities Table

Facility name and address	FEI	Responsibilities and profile code(s)	Status
Laurus Labs Limited, (VSP-2) (b)(4)	3011538548	(b)(4)	Approve - Based on Previous History

(b)(4)

Laurus Labs Limited (b)(4)			
(b)(4)	3007083664	(b)(4)	Approve - Based on PAI
Plot No. 21, Jawaharlal Nehru Pharma City Parawada, Visakhapatnam, Andhra Pradesh, India, 531021			
Laurus Labs Limited (b)(4)	3007083664	(b)(4)	Approve - Based on Previous History
Plot No. 18, Jawaharlal Nehru Pharma City Parawada, Visakhapatnam, Andhra Pradesh, India, 531021			
(b)(4)			Approve - Based on PAI (In lieu of PAI, documents assessed using 704(a)(4))
			(b)(4)
			Approve - Based on PAI (In lieu of PAI, documents assessed using 704(a)(4))

(b)(4)

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**Comparative Quantitative Batch Formula Composition
(Exhibit Batch vs Intended Commercial Batch)**

The comparative batch formula of exhibit batches and intended commercial batches of Sacubitril and Valsartan Tablets 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg is presented in below table:

Ingredients	Quality Standard	Exhibit Batch Size		Intended Commercial Batch Size	
		Quantity per batch (kg)	Quantity per batch %(w/w)	Quantity per batch (kg)	Quantity per batch %(w/w)
(b)(4)					
Sacubitril-Valsartan 3Na Complex ^s	In-House	(b)(4)			
Low-substituted hydroxypropylcellulose (b)(4)	USP-NF				
Microcrystalline Cellulose (b)(4)	USP-NF				
Crospovidone (b)(4)	USP-NF				
Silicon dioxide (b)(4)	USP-NF				
Magnesium Stearate (b)(4)	USP-NF				
(b)(4)					
(b)(4)					

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(b) (4)

V. List of Outstanding Information Request/Deficiencies:

Outstanding Deficiencies Collation Table
None

VI. Signature Block

Round#	Primary Name	Secondary & Other Names	Date of Completion	Assessment Outcome	Facility OMIR
1	Mesfin Abdi 11/12/2019	Jean Tang 12/04/2019	12/5/2019	IR	Withheld
2	Mesfin Abdi 02/13/2020	Jean Tang 02/19/2020	2/19/2020	IR	Withheld
3	Mesfin Abdi 03/03/2020	Jean Tang 03/13/2020	4/29/2020	Adequate	Withheld

	04/28/2020	04/29/2020			
4	Mesfin Abdi 12/18/2020	Jean Tang 12/23/2020	12/23/2020	Adequate	Approve
5	Md Abdullah A Mahmud	Zhaoyang Meng	11/03/2022	Adequate	Approve



Md Abdullah
Mahmud

Digitally signed by Md Abdullah Mahmud
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Zhaoyang
Meng

Digitally signed by Zhaoyang Meng
Date: 11/15/2022 12:36:11PM
GUID: 53725ca00005b7050cab6927e300151e

BIOPHARMACEUTICS ANDA REVIEW	
Application No.	ANDA-213676-ORIG-1
Applicant	Laurus Labs Limited
Product Name/ Strength(s)	Sacubitril and Valsartan Tablets/ 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg
Dosage Form/Route	(b)(4) Tablets/Oral
Indication	Reduce the risk of cardiovascular death and hospitalization for heart failure
Submission Date(s)	7/8/2019 – Original Submission 2/6/2020 – Response to Information Request
RLD/RS	Entresto® Tablets [N207620]
Primary Reviewer	Churg Chan, Pharm.D.
Secondary Reviewer	Om Anand, Ph.D.
Recommendation	Adequate

EXECUTIVE SUMMARY:

This Biopharmaceutics Review evaluates data supporting the adequacy of the proposed dissolution method and acceptance criteria for quality control testing of the proposed drug product.

Dissolution Method:

The Applicant proposes to use the same dissolution method for Sacubitril/Valsartan Tablets as

(b)(4)

Based on the provided information and data, the proposed dissolution method (Table 1) is deemed adequate for quality control testing of the proposed product. The Applicant’s originally proposed dissolution acceptance criteria were (b)(4) and therefore not acceptable. Based on the provided data, the Applicant was recommended via an Information Request dated January 3, 2020 to revise the dissolution acceptance criteria to (b)(4)

(b)(4)

(b)(4)

of the proposed drug product. In a response dated February 6, 2020, the Applicant accepted the FDA recommendation regarding the dissolution acceptance criterion for the 49 mg/51 mg and 97 mg/103 mg strengths, however, they proposed “NLT (b)(4) % (Q) of Sacubitril and Valsartan in 30 minutes” for the 24 mg/26 mg strength as well. Based on the totality of the information/data submitted, the newly proposed dissolution acceptance criterion and the response is acceptable.

¹ [FDA Recommended Dissolution Methods](#)

Table 1. Approved dissolution method and acceptance criteria²

Method Source	USP Apparatus	Speed	Medium	Volume/ Temperature	Recommended Acceptance Criteria
FDA – Database	II (Paddle)	50 RPM	pH 6.8 Phosphate Buffer	900 mL/ 37 ± 0.5°C	NLT % (Q) of Sacubitril in 30 minutes NLT % (Q) of Valsartan in 30 minutes

Recommendation:

From a Biopharmaceutics perspective, ANDA 213676 for the proposed Sacubitril/Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg, is recommended for **approval**.

² [Application 213676 - Sequence 0001 - Pharmaceutical Development Report](#)

BIOPHARMACEUTICS REVIEW

1. **Drug Substance Solubility:** The Applicant provided (b)(4)

(b)(4)

2. **Formulation:** The proposed product (b)(4)

(b)(4)

3. **Bioequivalence:** The Applicant performed *in vivo* pharmacokinetic studies using the 97 mg/103 mg strength of the proposed and RLD products in both fasting and fed conditions.⁶ Under fasting conditions, the T_{max} of Sacubitril and Valsartan were 0.71 and 2.14 hours, respectively.⁷ Under fed conditions, the T_{max} of Sacubitril and Valsartan were 1.83 hours and 3.31 hours, respectively.⁸ The Division of Bioequivalence/OGD will evaluate the bioequivalence study results and the biowaiver request.

4. **Dissolution Method:** (b)(4)

(b)(4)

The Applicant evaluated discriminating ability of the proposed dissolution method on changes of high-risk formulation variables (b)(4)

(b)(4)

The Applicant manufactured batches with (b)(4)

(b)(4)

The dissolution profiles generated (b)(4) (b)(4)

(b)(4)

(b)(4)

The dissolution profiles were similar across the formulations evaluated with the proposed dissolution method. However, based on the totality of the provided data and information, the proposed dissolution method is deemed adequate for quality control testing of the proposed product.

In an Information Request dated January 3, 2020, the Applicant was asked to submit dissolution data (b)(4)

³ [Application 213676 - Sequence 0001 - Quality Overall Summary - Drug Substance \(PDF\)](#)

⁴ [Application 213676 - Sequence 0001 - Description of Manufacturing Process and Process Controls](#)

⁵ [Application 213676 - Sequence 0001 - Description and Composition of the Drug Product](#)

⁶ [Application 213676 - Sequence 0001 - Tabular Listing of All Clinical Studies \(Pivotal Batch\)](#)

⁷ [Application 213676 - Sequence 0001 - Clinical Study Report Body - Fasting Study](#)

⁸ [Application 213676 - Sequence 0001 - Clinical Study Report Body - Fed Study](#)

(b)(4)

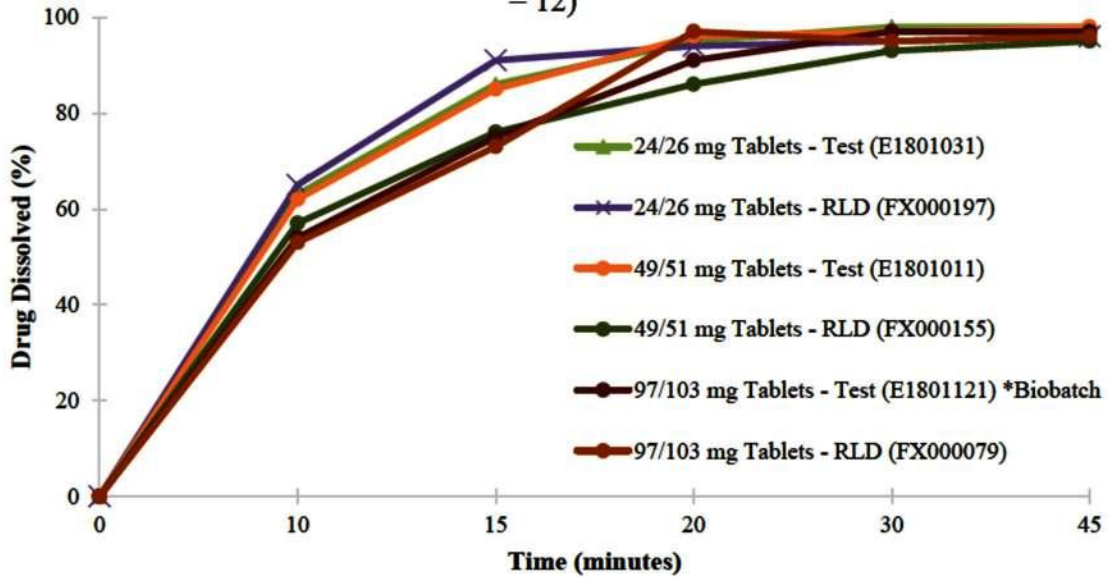
(b)(4)

(b)(4)

The Applicant proposed to continue using their original dissolution method for their proposed drug product [900 mL of pH 6.8 phosphate buffer using USP Apparatus II (Paddle) at 50 rpm].

5. Dissolution Data:¹¹

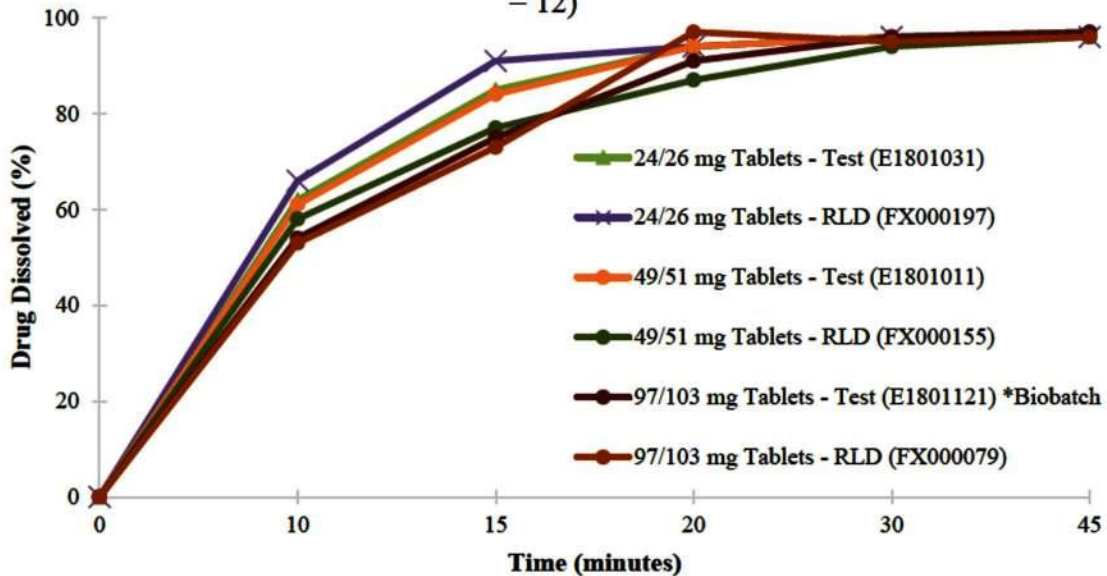
Figure 1. Summary of mean *in vitro* dissolution data for Sacubitril (*n* = 12)



¹⁰ [Application 213676 - Sequence 0007 - Comparative In-Vitro Dissolution Data](#)

¹¹ [Application 213676 - Sequence 0001 - Clinical Summary \(PDF\)](#)

Figure 2. Summary of mean *in vitro* dissolution data for Valsartan (*n* = 12)



- 6. Dissolution Acceptance Criteria:** The original dissolution acceptance criteria proposed by the Applicant (b)(4) was (b)(4) not supported by the data. The Applicant was recommended via an Information Request dated January 3, 2020 to implement the dissolution acceptance criteria of (b)(4) (b)(4) and “NLT (b)(4) % (Q) of Sacubitril and Valsartan at 30 minutes” for the 49 mg/51 mg and 97/103 mg strength tablets for the proposed drug product. In a response dated February 6, 2020, the Applicant accepted the FDA recommendation regarding the dissolution acceptance criterion for the 49 mg/51 mg and 97 mg/103 mg strengths, however, they proposed “NLT (b)(4) % (Q) of Sacubitril and Valsartan in 30 minutes” for the 24 mg/26 mg strength as well. The Applicant justified their proposition by reviewing data at (b)(4) and 30 minutes for all their exhibit batches and the RLD. Both the proposed and reference drug product have individual unit values (b)(4) % at the (b)(4) (b)(4) time point, (b)(4). Therefore, based on the totality of the provided data and information, the Applicant’s proposed acceptance criteria are acceptable.
- 7. Stability:** The Applicant provided stability data for exhibit batches of Sacubitril and Valsartan tablets for 6 months under long-term (25° ± 2°C/60% ± 5% RH) and accelerated (40° ± 2°C/75% ± 5% RH) conditions.¹² No significant changes in dissolution in stability were observed using the proposed dissolution method.
- 8. Dissolution Risk/Mitigation Assessment:** The biopharmaceutics and dissolution risk are relatively high because Sacubitril and Valsartan are considered (b)(4) per the

¹² [Application 213676 - Sequence 0001 - Stability Summary and Conclusion](#)

Applicant's BCS claims. The dissolution acceptance criteria are adequately selected to mitigate the risk of dissolution failure for the proposed drug product.

Biopharmaceutics Information Request

The following Biopharmaceutics Information Request (IR) comments were conveyed to the Applicant on January 3, 2020:

1. Based on the provided information and data, the proposed dissolution method (USP II at 50 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 (b)(4) dissolution acceptance criteria and therefore the proposed acceptance criterion is not acceptable. Implement the following acceptance criteria for your proposed product, Sacubitril and Valsartan Tablets:

(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.

2.

(b)(4)

(b)(4) Please submit dissolution data [(N=12, individual, mean, CV%)] for the bio-batch and at least one batch of other strengths using this new dissolution method (b)(4)

(b)(4)

please submit the information/data showing the suitability/discriminating ability of the proposed dissolution method for your proposed drug product.

The Applicant responded to the above Biopharmaceutics Information Request (IR) on February 6, 2020 and accepted the recommended dissolution acceptance criteria of $Q = \frac{1000}{1000}$ % at 30 minutes for the 49 mg/51 mg and 97 mg/103 mg strengths. The Applicant also proposed the same dissolution acceptance criterion of $Q = \frac{1000}{1000}$ % at 30 minutes for their 24 mg/26 mg strength. The Applicant provided dissolution data using the new FDA dissolution database method, however, they proposed to continue using their originally proposed dissolution method. Given the available data, the response is acceptable.



Churg
Chan

Digitally signed by Churg Chan
Date: 2/28/2020 07:37:19AM
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Om
Anand

Digitally signed by Om Anand
Date: 2/28/2020 10:00:25AM
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Stefen
Mcmillan

Digitally signed by Stefen Mcmillan
Date: 11/18/2022 11:52:15AM
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Marco A.
Bennett

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Date: 11/18/2022 11:50:16AM
GUID: 508da705000289bae41af5c5413d8455

MANUFACTURING INTEGRATED ASSESSMENT

Application ID	ANDA 213676
Drug Product Name	Sacubitril and Valsartan Tablets
Strengths	24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg
Dosage Form	Tablets
Administration Route	Oral
Indication	(b)(4)
Applicant Name	Laurus Labs Limited
RLD Number	207620

Note: Updates in this review cycle (R05, Amend-16) is typed in purple text.

Both Process and Facilities remain Adequate as assessed in previous cycle (A 213676-ORIG-AMEND-12).

(b)(4)

(b)(4) All facilities are found Adequate. The Overall Manufacturing Inspection Recommendation is Approve.

The latest Manufacturing Integrated Assessment (ANDA 213676-ORIG-1-AMEND-09, added on Dec 28, 2020) was not archived in Panorama. Therefore, the IQA document is uploaded in current review cycle for archival purpose only.

I. Manufacturing Summary

Facility Assessment Recommendation: Adequate

Process Assessment Recommendation: Adequate

Assessment Summary:

Sacubitril and Valsartan Tablets 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg is manufactured using (b)(4)

(b)(4)

The DS manufacturer, DP manufacturer, Critical Intermediate manufacturer and external testing facility are recommended for approval based on compliance history, acceptable profile codes and experience in the proposed responsibilities.

List Submissions being assessed (Table):

Document Description (SD #)	Date Received

Original (SD# 0001)	07/08/2019
Response to IR (SD# 0003)	09/16/2019
Response to IR (SD#0007)	02/06/2020
Response to IR (SD#0008)	03/02/2020
Response to CR (SD#0009)	07/01/2020
Response to CR (SD #16)	03/17/2022

Highlight Key Issues from Last Cycle and Their Resolution: None

Concise Description of Outstanding Issues (List bullet points with key information and update as needed): None

Highlight Key Issues from Last Cycle and Their Resolution: 1st Cycle

Review #1

(b) (4)

Review #2

(b)(4)

Concise Description of Outstanding Issues (List bullet points with key information and update as needed):

- None

List Number of Comparability Protocols: None

1. Lifecycle Management Considerations

Post-approval inspection?	No
Lifecycle considerations	No
Choose an item.	

2. Facilities Table

Facility name and address	FEI	Responsibilities and profile code(s)	Status
Laurus Labs Limited, (b)(4) (b)(4)	3011538548	(b)(4)	Approve - Based on Previous History

Plot No. 19, 20 and 21, Western Sector, APSEZ, Atchutapuram , Visakhapatnam, Andhra Pradesh, India, 531011		(b)(4)	
Laurus Labs Limited (b)(4) (b)(4)	3007083664		Approve - Based on PAI
Plot No. 21, Jawaharlal Nehru Pharma City Parawada, Visakhapatnam, Andhra Pradesh , India, 531021			Approve - Based on Previous History
Laurus Labs Limited (b)(4) Plot No. 18, Jawaharlal Nehru Pharma City Parawada, Visakhapatnam, Andhra Pradesh, India, 531021	3007083664		Approve - Based on PAI (In lieu of PAI, documents assessed using 704(a)(4))
(b)(4)			(b)(4)
			Approve - Based on PAI (In lieu of PAI, documents assessed using 704(a)(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.

**Comparative Quantitative Batch Formula Composition
(Exhibit Batch vs Intended Commercial Batch)**

The comparative batch formula of exhibit batches and intended commercial batches of Sacubitril and Valsartan Tablets 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg is presented in below table:

Ingredients	Quality Standard	Exhibit Batch Size (b)(4)		Intended Commercial Batch Size (b)(4)	
		Quantity per batch (kg)	Quantity per batch %(w/w)	Quantity per batch (kg)	Quantity per batch %(w/w)
Intra-granular Part					
Sacubitril-Valsartan 3Na Complex ^s	In-House	(b)(4)			
Low-substituted hydroxypropylcellulose (b)(4)	USP-NF				
Microcrystalline Cellulose (b)(4)	USP-NF				
Croscovidone (b)(4)	USP-NF				
Silicon dioxide (b)(4)	USP-NF				
Magnesium Stearate (b)(4)	USP-NF				
(b)(4)					
Total Weight	(b)(4)	(b)(4)	100.00	(b)(4)	100.00
(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)

V. List of Outstanding Information Request/Deficiencies:

Outstanding Deficiencies Collation Table
None

VI. Signature Block

Round#	Primary Name	Secondary & Other Names	Date of Completion	Assessment Outcome	Facility OMIR
1	Mesfin Abdi 11/12/2019	Jean Tang 12/04/2019	12/5/2019	IR	Withheld
2	Mesfin Abdi 02/13/2020	Jean Tang 02/19/2020	2/19/2020	IR	Withheld
3	Mesfin Abdi 03/03/2020	Jean Tang 03/13/2020	4/29/2020	Adequate	Withheld

	04/28/2020	04/29/2020			
4	Mesfin Abdi 12/18/2020	Jean Tang 12/23/2020	12/23/2020	Adequate	Approve
5	Md Abdullah A Mahmud	Zhaoyang Meng	11/03/2022	Adequate	Approve



Md Abdullah
Mahmud

Digitally signed by Md Abdullah Mahmud
Date: 11/14/2022 07:26:38PM
GUID: 5c5b4834002884b42520496954285e3c



Zhaoyang
Meng

Digitally signed by Zhaoyang Meng
Date: 11/15/2022 12:36:11PM
GUID: 53725ca00005b7050cab6927e300151e

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> <i><u>AND</u></i> • <i>OGD has deficiencies (e.g., Bioequivalence, Labeling, etc.)</i>

ANDA 213676 Assessment #4

Drug Product Name	Sacubitril and Valsartan Tablets
Dosage Form	Capsules
Strength	24mg/26mg, 49mg/51mg and 97mg/103mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Laurus Labs Limited
US agent, if applicable	PharmaQ, Inc.

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original/Initial Submission	07/08/2019	Quality
Amendment Correspondence/Amendment Verification Statement - Quality/Response to Information Request	09/16/2019	Quality
Amendment Correspondence/Amendment Verification Statement; Quality/Response to Discipline Review Letter	02/06/2020	Quality
Quality/Response to Information Request; Amendment Correspondence/Amendment Verification Statement	03/02/2020	Quality
Resubmission/After Action- Complete; Amendment Correspondence/Amendment Verification Statement; Bioequivalence/Other; Quality/Quality Information; Quality/Facility Information	07/1/2020	Quality
Resubmission/After Action- Complete	05/03/2021	Quality
Submission(s) Assessed	Document Date	Discipline(s) Affected
Resubmission/After Action- Complete	11/26/2021	DP

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Product/Drug substance	Xihong Wang	Marco A. Bennett
Facility	Jim Chen	
Biopharmaceutics	NAI	NAI

Regulatory Business Process Manager	Helina Zenebe
Application Technical Lead	Marco A. Bennett

QUALITY ASSESMENT DATA SHEET

[IQA ANDA Assessment Guide Reference](#)

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Reviewed	Comments
33647	II	Laurus Labs Limited	Sacubitril-Valsartan 3Na Complex	Adequate	09/16/2021	Xianru Sun
Other DMF: ☐ N/A ☒ (See Below)						
(b)(4)	III	(b)(4)	(b)(4)			
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					

(b)(4)	III	(b)(4)			
	IV				

B. OTHER DOCUMENTS: IND, RLD, RS, Approved ANDA

Document	Application Number	Brand Name	Description
NDA (RLD)	NDA 207620	ENTRESTO® (sacubitril and valsartan) tablets	ENTRESTO® (sacubitril and valsartan) tablets 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg, manufactured by Novartis Pharmaceuticals Corporation. Approval date: 07/07/2015

2. CONSULTS: None

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology				
CDRH-ODE				
CDRH-OC				
Clinical				
Other				

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 OPQ action recommendation is a CR-Major owing to DP being a Major.

II. QUALITY ASSESSMENT OVERVIEW

III. A. DP OVERALL RECOMMENDATION: Inadequate-Major

Drug Substance: Adequate

1. Provide Justification, if **Major**: (Click link to view [Justification Statements](#))

None

2. Insert additional **Major** justification below (if necessary)

None

The Drug Substance assessment is adequate.

Drug Product: 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)

None.

The Drug Product assessment is CR-Major please see below for deficiency.

Labeling: Adequate

The OPQ Labeling assessment is adequate.

B. Manufacturing:

a. Process: Adequate

1. Provide Justification, if **Major**: (Click link to view [Justification Statements](#))

None

2. Insert additional **Major** justification below (if necessary)

None

The Manufacturing Process assessment is adequate.

b. Facilities: Adequate

1. Provide Justification, if **Major**: (Click link to view [Justification Statements](#))

None

2. Insert additional **Major** justification below (if necessary)

None

The Manufacturing Facilities assessment is adequate.

C. Biopharmaceuticals: Adequate

1. Provide Justification, if **Major**: (Click link to view [Justification Statements](#))

None

2. Insert additional **Major** justification below (if necessary)

None

The Biopharmaceuticals assessment is adequate.

D. Microbiology: Choose an item. N/A

E. List of Deficiencies for Complete Response

Overall Quality Deficiencies - Optional (*Deficiencies that affect multiple sub-disciplines*): *None*

I. Drug Substance Deficiencies

None

II. Drug Product Deficiencies

1.

(b) (4)

III. Labeling Deficiencies (*Please contact OGD if you identify any Labeling deficiencies with your comments*)

IV. Manufacturing Deficiencies:

None

V. Biopharmaceutics Deficiencies

None

VI. Microbiology Deficiencies

VII. 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*)

In addition to responding to the deficiencies presented above, please note and acknowledge the following comment(s) in your response: **None**

Application Technical Lead Name and Date: Marco A. Bennett, 02.10.2022



Marco A.
Bennett

Digitally signed by Marco A. Bennett

Date: 2/10/2022 05:50:58PM

GUID: 508da705000289bae41af5c5413d8455



DRUG PRODUCT QUALITY ASSESSMENT

ANDA 213676 (Review Cycle # 04)

Sacubitril and Valsartan Tablets,

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

CR-Major Justification: 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.

Xihong Wang

Division of Immediate Release Products I/Branch II

Office of Lifecycle Drug Products

Office of Pharmaceutical Quality

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ANDA 213676 (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	Laurus Labs Limited Second Floor, Serene Chambers, Road No.7, Banjara Hills Hyderabad, Telangana India. 500034
Drug Product Manufacturer	(b) (4)
US agent, if applicable	☐ N/A ☒ (See Below) Sharath Koripally, Senior Director RA, QA & PV Laurus Generics Inc. 400 Connell Drive, Suite 5200 Berkeley Heights, NJ 07922 Tel: (718) 510-6822 Email: sharath.koripally@laurusgenerics.com
Proposed Indication	(b) (4)

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original (Subject of review #1)	07/08/2019	All
Amendment: Response to DRL-Labeling dated 10/25/19 (Subject of review #1)	11/07/2019	Labeling
Amendment: Response to DRL-Labeling dated 01/03/20 (Subject of review #1, IR#1)	02/06/2020	DP, Biopharm, Process
Amendment: Response to IR letter from the agency (Biopharm) dated 02/20/2020 (Subject of Biopharm review)	03/02/2020	Biopharm
Amendment: Response to CR letter from the agency dated 05/04/2020 (Subject of review #2)	07/01/2020	DP, Facility, BE
Amendment: Response to CR letter from the agency dated 02/22/2021 (Subject of review #3)	05/03/2021	DP, Labeling
General Correspondence: Change in US agent (Updated in the table above)	08/02/2021	
Amendment: Response to CR letter from the agency dated 10/04/2021 (Subject of Labeling review)	11/26/2021	Labeling

QUALITY ASSESMENT DATA SHEET

[IQA ANDA Assessment Guide Reference](#)

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Reviewed	Comments
33647	II	Laurus Labs Limited	Sacubitril-Valsartan 3Na Complex	Adequate	09/16/2021	Xianru Sun
Other DMF: ☐ N/A ☒ (See Below)						
(b)(4)	III	(b)(4)	(b)(4)			
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	IV					

			(b)(4)			

B. OTHER DOCUMENTS: IND, RLD, RS, Approved ANDA

Document	Application Number	Brand Name	Description
NDA (RLD)	NDA 207620	ENTRESTO® (sacubitril and valsartan) tablets	ENTRESTO® (sacubitril and valsartan) tablets 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg, manufactured by Novartis Pharmaceuticals Corporation. Approval date: 07/07/2015

2. CONSULTS: None

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology				
CDRH-ODE				
CDRH-OC				
Clinical				
Other				

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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.

CHAPTER I: DRUG SUBSTANCE

[IQA ANDA Assessment Guide Reference](#)

Drug Substance Name	Sacubitril-Valsartan 3Na Complex
DMF Number (If Applicable)	033647
DMF Status	Inadequate - Major
DMF Holder	Laurus Labs Limited

Overall Assessment Recommendation for DS:

DRL

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.

Highlight Key Issues from Last Cycle and Their Resolution:

N/A - This is the review of original ANDA

Concise Description of Outstanding Issues:

Choose an item.

Select Number of Approved Comparability Protocols: 0

S.1 GENERAL INFORMATION

Nomenclature/Chemical name	:	Tri sodium [3-((1 <i>S</i> ,3 <i>R</i>)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl -1-butylcarbamoyl)propionate-(<i>S</i>)-3'-methyl-2'-(pentanoyl {2''-(tetrazol-5-ylate) biphenyl-4'-ylmethyl} amino)butyrate] (or) Tri sodium (4-[[[(1 <i>S</i> ,3 <i>R</i>)-1-([1,1'-biphenyl-4-ylmethyl-4-ethoxy-3-methyl-4-oxobutyl]amino)-4-oxobutanoate)(N-pentanoyl-N-{2'-(1 <i>H</i> -tetrazol-1-id-5-yl) [1,1'-biphenyl]-4-yl]methyl}-L-valinate)			
		<table border="1"> <thead> <tr> <th>Sacubitril</th> <th>Valsartan</th> </tr> </thead> <tbody> <tr> <td>4-[[[(1<i>S</i>,3<i>R</i>)-1-([1,1'-Biphenyl] -4-ylmethyl)-4-ethoxy -3-methyl-4-oxobutyl]amino]-4-oxobutanoic acid</td> <td>N-Pentanoyl-N-{[2'-(1<i>H</i>-tetrazol-5-yl)[1,1'-biphenyl] -4-yl]methyl}-L-valine</td> </tr> </tbody> </table>	Sacubitril	Valsartan	4-[[[(1 <i>S</i> ,3 <i>R</i>)-1-([1,1'-Biphenyl] -4-ylmethyl)-4-ethoxy -3-methyl-4-oxobutyl]amino]-4-oxobutanoic acid
Sacubitril	Valsartan				
4-[[[(1 <i>S</i> ,3 <i>R</i>)-1-([1,1'-Biphenyl] -4-ylmethyl)-4-ethoxy -3-methyl-4-oxobutyl]amino]-4-oxobutanoic acid	N-Pentanoyl-N-{[2'-(1 <i>H</i> -tetrazol-5-yl)[1,1'-biphenyl] -4-yl]methyl}-L-valine				
International Non-proprietary Name (INN)	:	Not reported			
Compendial Name (WHO)	:	Not reported			
United States Adopted Name (USAN)	:	Sacubitril and valsartan			
Molecular Structure	:	Sacubitril-Valsartan 3Na Complex			
Molecular Formula	:	C ₄₈ H ₅₅ N ₆ O ₈ .3Na			
CAS number	:	936623-90-4			
Relative Molecular mass	:	912.95			
Pharmacological Class	:	Angiotensin II receptor and neprilysin inhibitor for the treatment of chronic heart failure (NYHA Class II-IV) and reduced ejection fraction.			

Physical form	:	White to off-white solid
(b)(4)		

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CHAPTER II: DRUG PRODUCT

[IQA ANDA Assessment Guide Reference](#)

Overall Assessment Recommendation: **Discipline Review Letter (DRL)**

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:

Drug Product CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Review Cycle #2	Comments*
Physical stability (solid state)	36 Medium	(b)(4)	Low	(b)(4)
Chemical Stability	48 Medium		Low	
Assay	18 Low		Low	
Content uniformity	24 Low			

		(b)(4)		(b)(4)
Microbial limits	9 Low		Low	
Dissolution	48 Medium			

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 the 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. Biopharm review is inadequate.*
- *Elemental impurity compliance with ICH Q3D – status: Adequate*
- *Number of Comparability protocols included: 0*

RLD versus Generic Product – NOT FOR FOIA

(b) (4)

* For repacking purpose only

P.1 DESCRIPTION AND COMPOSITION

Component/Composition of Sacubitril and Valsartan Tablets 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg

Ingredients	Compendial Reference	Pharmaceutical Function	24mg/26mg	49mg/51mg	97mg/103mg	%w/w
			(mg/ Tablet)			
Intra-granular materials						
Sacubitril-Valsartan 3Na Complex [^]	In-House	Active Ingredient	(b)(4)	(b)(4)	(b)(4)	(b)(4)
Low-substituted hydroxypropylcellulose (b)(4)	USP-NF	(b)(4)				
Microcrystalline Cellulose (b)(4)	USP-NF					
Croscopovidone (b)(4)	USP-NF					
Silicon dioxide (b)(4)	USP-NF					
Magnesium Stearate (b)(4)	USP-NF					
(b)(4)						
Weight of Coated Tablet			103.000	206.000	412.000	100.000

(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)

R REGIONAL INFORMATION

Environmental

- Laurus Labs Limited states that for this Abbreviated New Drug Application (ANDA) we are subject to a categorical exclusion from the requirement to prepare an Environmental Assessment Statement, as per 21 CFR § 25.30, 25.31, 25.33 and 25.15 (d).
- This ANDA is for the drug product which will not be indicated for administration at a higher dose level, nor for a longer duration, or for different indications than those that are in effect. No extraordinary circumstances, as outlined in 21 CFR § 25.21, exist. Hence, a categorical exclusion from the requirement to prepare an Environmental Assessment is hereby requested.
- Also, Laurus Labs Limited, hereby states that we are in compliance with all federal, state and local environmental laws.

Assessment:
Adequate

Adequate

Methods Validation or Verification Package

Assessment:

Adequate

Comparability Protocols

Assessment:
N/A

Choose an item.

Lifecycle Management Considerations

DRUG PRODUCT LIST OF DEFICIENCIES

1.

2.

3.

4.

(b) (4)

(b) (4)

5.

6.

7.

(b) (4)

8.

9.

10

11

(b) (4)

CHAPTER III: ENVIRONMENTAL

[IQA ANDA Assessment Guide Reference](#)

R REGIONAL INFORMATION

Environmental

- Laurus Labs Limited states that for this Abbreviated New Drug Application (ANDA) we are subject to a categorical exclusion from the requirement to prepare an Environmental Assessment Statement, as per 21 CFR § 25.30, 25.31, 25.33 and 25.15 (d).
- This ANDA is for the drug product which will not be indicated for administration at a higher dose level, nor for a longer duration, or for different indications than those that are in effect. No extraordinary circumstances, as outlined in 21 CFR § 25.21, exist. Hence, a categorical exclusion from the requirement to prepare an Environmental Assessment is hereby requested.
- Also, Laurus Labs Limited, hereby states that we are in compliance with all federal, state and local environmental laws.

Assessment:
Adequate

Adequate

CHAPTER IV: LABELING

[IQA ANDA Assessment Guide Reference](#)

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	Dimension (mm) (Length x Width)	Imprint Code
24mg/26mg	9.11x 5.08	Violet white color, oval, biconvex film-coated tablets debossed with "S5" on one side and plain on the other side.
49mg/51mg	12.75 x 5.90	Pale yellow color, oval, biconvex film-coated tablets debossed with "S1" on one side and plain on the other side.
97mg/103mg	12.57 x 6.85	Light pink color, oval, biconvex film-coated tablets debossed with "S2" on one side and plain on the other side.

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

A. Drug Substance Deficiencies

None

B. Drug Product Deficiencies

1.

(b) (4)

C. Labeling Deficiencies

None

(END OF DRUG PRODUCT QUALITY ASSESSMENT)

Signature Block:

Primary DP Assessor: *Xihong Wang*

Date: 12/19/19;
3/31/2020;
1/22/2021
7/1/2021,
09/16/2021;
01/27/2022,
02/04/2022

Secondary DP Assessor: *Marco Bennett*

Date: 12/19/2019;
04.01.2020;
04.14.2020;
01.22.2021;
07.02.2021;
09.17.2021;
01.31.2022;
02.04.2022



Marco A.
Bennett

Digitally signed by Marco A. Bennett

Date: 2/04/2022 11:53:32AM

GUID: 508da705000289bae41af5c5413d8455



Xihong
Wang

Digitally signed by Xihong Wang

Date: 2/04/2022 01:07:01PM

GUID: 508da7410002ba99af7b0597dc38d164

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 213676
Assessment #3

Drug Product Name	Sacubitril and Valsartan Tablets, 24mg/26mg, 49mg/51mg and 97mg/103mg
Dosage Form	Capsules
Strength	24mg/26mg, 49mg/51mg and 97mg/103mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Laurus Labs Limited
US agent, if applicable	PharmaQ, Inc.

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original/Initial Submission	07/08/2019	Quality
Amendment Correspondence/Amendment Verification Statement - Quality/Response to Information Request	09/16/2019	Quality
Amendment Correspondence/Amendment Verification Statement; Quality/Response to Discipline Review Letter	02/06/2020	Quality
Quality/Response to Information Request; Amendment Correspondence/Amendment Verification Statement	03/02/2020	Quality
Resubmission/After Action- Complete; Amendment Correspondence/Amendment Verification Statement; Bioequivalence/Other; Quality/Quality Information; Quality/Facility Information	07/1/2020	Quality
Resubmission/After Action- Complete	05/03/2021	Quality
Multiple category submission	08/02/2021	Quality

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Product/Drug substance	Xihong Wang	Marco A. Bennett
Facility	Mesfin Abdi	Jean Tang
Biopharmaceutics	Churg Chan	Om Anand
Regulatory Business Process Manager	Helina Zenebe	
Application Technical Lead	Marco A. Bennett	

QUALITY ASSESMENT DATA SHEET

[IQA ANDA Assessment Guide Reference](#)

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Reviewed	Comments
33647	II	Laurus Labs Limited	Sacubitril-Valsartan 3Na Complex	Adequate	09/16/2021	Xianru Sun

Other DMF: N/A (See Below)

(b)(4)	III	(b)(4)				
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					

(b)(4)	III	(b)(4)			
	IV				

B. OTHER DOCUMENTS: IND, RLD, RS, Approved ANDA

Document	Application Number	Brand Name	Description
NDA (RLD)	NDA 207620	ENTRESTO® (sacubitril and valsartan) tablets	ENTRESTO® (sacubitril and valsartan) tablets 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg, manufactured by Novartis Pharmaceuticals Corporation. Approval date: 07/07/2015

2. CONSULTS: None

EXECUTIVE SUMMARY (APPROVALS ONLY)

For more details about the items in this template, please see the [Executive Summary \(Approvals Only\) chapter of the ANDA IQA Guide](#)

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

OPQ recommends approval of this ANDA on the basis that OLDP (CMC), Process, Biopharmaceutics and Facilities are all adequate a summary paragraph outlining reasons for OPQ action recommendation.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The drug product Sacubitril and Valsartan Tablets, 24mg/26mg, 49mg/51mg and 97mg/103mg. The drug product is not a compendial item.

Is the Firm's proposed recommended dissolution method/specification found acceptable by Biopharmaceutics?	☒ Yes ☐ No ☐ N/A
Are there comparability protocols provided? If yes, how many?	☐ Yes How many: _____ ☒ No
If USP monograph exists, do the specifications comply with the current USP?	☐ Yes ☒ DS* ☐ DP ☐ No ☒ N/A
Is the application compliant with USP <232/233> requirements or ICH Q3D recommendations (regarding elemental impurities)?	☒ Yes ☐ No ☐ N/A

**USP Monograph exists for Valsartan DS only*

Proposed Indication(s) including Intended Patient Population	(b)(4)
Duration of Treatment	Rx
Maximum Daily Dose	Sacubitril sodium 194mg; Valsartan disodium: 206mg
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance General Information

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.

The DS manufacturer, DP manufacturer, Critical Intermediate manufacturer and external testing facility are recommended for approval based on compliance history, acceptable profile codes and experience in the proposed responsibilities.

Facilities assessment

A review of the application and inspectional documents indicate there are no significant, outstanding manufacturing risks that prevent approval of this application from a GMP facility perspective. Based on the firm inspection history and EIR reviews, the manufacturing facilities as listed below for ANDA 212490 are found to be acceptable.

Update per amendment dated 6/1/2020:

(b)(4)

Facility name and address	FEI	Responsibilities and profile code(s)	Status
Laurus Labs Limited, (b)(4) (b)(4) Plot No. 19, 20 and 21, Western Sector, APSEZ, Atchutapuram, Visakhapatnam, Andhra Pradesh, India, 531011	3011538548	(b)(4)	Approve - Based on Previous History
Laurus Labs Limited (b)(4) (b)(4) Plot No. 21, Jawaharlal Nehru Pharma City Parawada, Visakhapatnam, Andhra Pradesh, India, 531021	3007083664		Approve - Based on PAI
Laurus Labs Limited (b)(4) Plot No. 18, Jawaharlal Nehru Pharma City Parawada, Visakhapatnam, Andhra Pradesh, India, 531021	3007083664		Approve - Based on Previous History
(b)(4)			Approve - Based on PAI (In lieu of PAI, documents assessed using 704(a)(4))

(b) (4)

(b) (4)

Approve - Based on PAI (In lieu of PAI, documents assessed using 704(a)(4))

The OPMA assessment is adequate.

Biopharmaceutics Summary

(b) (4)

Based on the provided information and data, the proposed dissolution method (Table 1) is deemed adequate for quality control testing of the proposed product. The Applicant's originally proposed dissolution acceptance criteria were (b)(4) not acceptable. Based on the provided data, the Applicant was recommended via an Information Request dated January 3, 2020 to revise the dissolution acceptance criteria to (b)(4)

(b)(4) "NLT (b)(4) % (Q) of Sacubitril and Valsartan in 30 minutes" for the 49 mg/51 mg and 97 mg/103 mg strengths of the proposed drug product. In a response dated February 6, 2020, the Applicant accepted the FDA recommendation regarding the dissolution acceptance criterion for the 49 mg/51 mg and 97 mg/103 mg strengths, however, they proposed "NLT (b)(4) % (Q) of Sacubitril and Valsartan in 30 minutes" for the 24 mg/26 mg strength as well. Based on the totality of the information/data submitted, the newly proposed dissolution acceptance criterion and the response is acceptable.

From a Biopharmaceutics perspective, ANDA 213676 for the proposed Sacubitril/Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg, is recommended for approval.

Approved dissolution method and acceptance criterion

Method Source	USP Apparatus	Speed	Medium	Volume/ Temperature	Recommended Acceptance Criteria

FDA – Database	II (Paddle)	50 RPM	pH 6.8 Phosphate Buffer	900 mL/ 37 ± 0.5°C	NLT (b)(4) % (Q) of Sacubitril in 30 minutes NLT (b)(4) % (Q) of Valsartan in 30 minutes

The Biopharmaceutics assessment is adequate.

C. Risk Assessment

Drug Product CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Review Cycle #2	Comments*
Physical stability (solid state)	36 Medium	(b)(4)	Low	(b)(4)
Chemical Stability	48 Medium		Low	
Assay	18 Low		Low	
Content uniformity	24 Low		Low	
Microbial limits	9 Low		Low	
Dissolution	48 Medium		Low	

Application Technical Lead Name and Date: Marco A. Bennett, 09.22.2021



Marco A.
Bennett

Digitally signed by Marco A. Bennett

Date: 9/22/2021 09:20:10AM

GUID: 508da705000289bae41af5c5413d8455



**U.S. FOOD & DRUG
ADMINISTRATION**

DRUG PRODUCT QUALITY ASSESSMENT

ANDA 213676 (Review Cycle # 03)

Sacubitril and Valsartan Tablets,

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

Xihong Wang

Division of Immediate Release Products I/Branch II

Office of Lifecycle Drug Products

Office of Pharmaceutical Quality

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ANDA 213676 (Assessment Cycle # 03)

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	Laurus Labs Limited Second Floor, Serene Chambers, Road No.7, Banjara Hills Hyderabad, Telangana India, 500034
Drug Product Manufacturer	(b) (4)
US agent, if applicable	☐ N/A ☒ (See Below) Sharath Koripally, Senior Director RA, QA & PV Laurus Generics Inc. 400 Connell Drive, Suite 5200 Berkeley Heights, NJ 07922 Tel: (718) 510-6822 Email: sharath.koripally@laurusgenerics.com
Proposed Indication	(b) (4)

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original (Subject of review #1)	07/08/2019	All
Amendment: Response to DRL-Labeling dated 10/25/19 (Subject of review #1)	11/07/2019	Labeling
Amendment: Response to DRL-Labeling dated 01/03/20 (Subject of review #1, IR#1)	02/06/2020	DP, Biopharm, Process
Amendment: Response to IR letter from the agency (Biopharm) dated 02/20/2020 (Subject of Biopharm review)	03/02/2020	Biopharm
Amendment: Response to CR letter from the agency dated 05/04/2020 (Subject of review #2)	07/01/2020	DP, Facility, BE
Amendment: Response to CR letter from the agency dated 02/22/2021 (Subject of review #3)	05/03/2021	DP, Labeling
General Correspondence: Change in US agent (Updated in the table above)	08/02/2021	

QUALITY ASSESMENT DATA SHEET

[IQA ANDA Assessment Guide Reference](#)

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Reviewed	Comments
33647	II	Laurus Labs Limited	Sacubitril-Valsartan 3Na Complex	Adequate	09/16/2021	Xianru Sun
Other DMF: ☐ N/A ☒ (See Below)						
(b)(4)	III	(b)(4)	(b)(4)			
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	IV					

			(b)(4)		

B. OTHER DOCUMENTS: IND, RLD, RS, Approved ANDA

Document	Application Number	Brand Name	Description
NDA (RLD)	NDA 207620	ENTRESTO® (sacubitril and valsartan) tablets	ENTRESTO® (sacubitril and valsartan) tablets 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg, manufactured by Novartis Pharmaceuticals Corporation. Approval date: 07/07/2015

2. CONSULTS: None

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology				
CDRH-ODE				
CDRH-OC				
Clinical				
Other				

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(b) (4)

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CHAPTER I: DRUG SUBSTANCE

[IQA ANDA Assessment Guide Reference](#)

Drug Substance Name	Sacubitril-Valsartan 3Na Complex
DMF Number (If Applicable)	033647
DMF Status	Inadequate - Major
DMF Holder	Laurus Labs Limited

Overall Assessment Recommendation for DS:

DRL

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.

Highlight Key Issues from Last Cycle and Their Resolution:

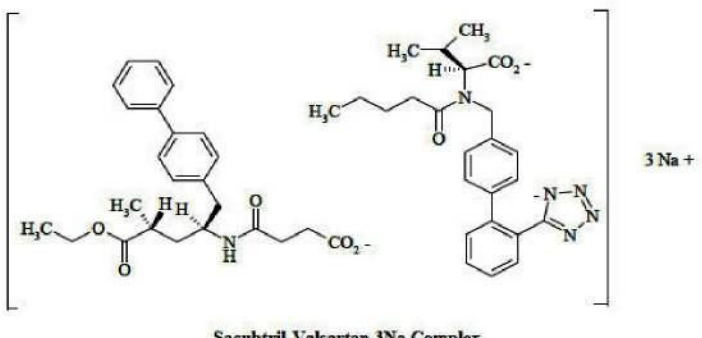
N/A - This is the review of original ANDA

Concise Description of Outstanding Issues:

Choose an item.

Select Number of Approved Comparability Protocols: 0

S.1 GENERAL INFORMATION

Nomenclature/Chemical name	: Tri sodium [3-((1 <i>S</i> ,3 <i>R</i>)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl -1-butylcarbamoyl)propionate-(<i>S</i>)-3'-methyl-2'-(pentanoyl {2''-(tetrazol-5-ylate) biphenyl-4'-ylmethyl} amino)butyrate]				
	(or) Tri sodium (4-[[[(1 <i>S</i> ,3 <i>R</i>)-1-([1,1'-biphenyl-4-ylmethyl-4-ethoxy-3-methyl-4-oxobutyl]amino)-4-oxobutanoate)(N-pentanoyl-N-{2'-(1 <i>H</i> -tetrazol-1-id-5-yl) [1,1'-biphenyl]-4-yl]methyl}-L-valinate)				
	<table border="1"> <thead> <tr> <th>Sacubitril</th> <th>Valsartan</th> </tr> </thead> <tbody> <tr> <td>4-[[[(1<i>S</i>,3<i>R</i>)-1-([1,1'-Biphenyl] -4-ylmethyl)-4-ethoxy -3-methyl-4-oxobutyl]amino]-4-oxobutanoic acid</td> <td>N-Pentanoyl-N-{[2'-(1<i>H</i>-tetrazol-5-yl)[1,1'-biphenyl] -4-yl]methyl}-L-valine</td> </tr> </tbody> </table>	Sacubitril	Valsartan	4-[[[(1 <i>S</i> ,3 <i>R</i>)-1-([1,1'-Biphenyl] -4-ylmethyl)-4-ethoxy -3-methyl-4-oxobutyl]amino]-4-oxobutanoic acid	N-Pentanoyl-N-{[2'-(1 <i>H</i> -tetrazol-5-yl)[1,1'-biphenyl] -4-yl]methyl}-L-valine
Sacubitril	Valsartan				
4-[[[(1 <i>S</i> ,3 <i>R</i>)-1-([1,1'-Biphenyl] -4-ylmethyl)-4-ethoxy -3-methyl-4-oxobutyl]amino]-4-oxobutanoic acid	N-Pentanoyl-N-{[2'-(1 <i>H</i> -tetrazol-5-yl)[1,1'-biphenyl] -4-yl]methyl}-L-valine				
International Non-proprietary Name (INN)	: Not reported				
Compendial Name (WHO)	: Not reported				
United States Adopted Name (USAN)	: Sacubitril and valsartan				
Molecular Structure	:  Sacubitril-Valsartan 3Na Complex				
Molecular Formula	: C ₄₈ H ₅₅ N ₆ O ₈ .3Na				
CAS number	: 936623-90-4				
Relative Molecular mass	: 912.95				
Pharmacological Class	: Angiotensin II receptor and neprilysin inhibitor for the treatment of chronic heart failure (NYHA Class II-IV) and reduced ejection fraction.				

Physical form	: White to off-white solid
	(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.

Assessment:

Adequate

(b) (4)

Assessment:
N/A

Choose an item.

R REGIONAL INFORMATION

Comparability Protocols N/A (See Below)

Assessment:

Choose an item.

Lifecycle Management Considerations

DRUG SUBSTANCE LIST OF DEFICIENCIES:

- 1.
- 2.
- 3.
- 4.

(b) (4)

CHAPTER II: DRUG PRODUCT

[IQA ANDA Assessment Guide Reference](#)

Overall Assessment Recommendation: **Discipline Review Letter (DRL)**

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:

Drug Product CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Review Cycle #2	Comments*
Physical stability (solid state)	36 Medium	(b)(4)	Low	(b)(4)
Chemical Stability	48 Medium		Low	
Assay	18 Low		Low	
Content uniformity	24 Low			

		(b)(4)		(b)(4)
Microbial limits	9 Low		Low	
Dissolution	48 Medium			

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 the 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. Biopharm review is inadequate.*
- *Elemental impurity compliance with ICH Q3D – status: Adequate*
- *Number of Comparability protocols included: 0*

RLD versus Generic Product – NOT FOR FOIA

(b) (4)

* For repacking purpose only

P.1 DESCRIPTION AND COMPOSITION

Component/Composition of Sacubitril and Valsartan Tablets 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg

Ingredients	Compendial Reference	Pharmaceutical Function	24mg/ 26mg	49mg/ 51mg	97mg/ 103mg	%w/w
			(mg/ Tablet)			
Intra-granular materials						
Sacubitril-Valsartan 3Na Complex [^]	In-House	Active Ingredient	(b)(4)			
Low-substituted hydroxypropylcellulose (b)(4)	USP-NF	(b)(4)				
Microcrystalline Cellulose (b)(4)	USP-NF					
Crospovidone (b)(4)	USP-NF					
Silicon dioxide (b)(4)	USP-NF					
Magnesium Stearate (b)(4)	USP-NF					
(b)(4)						
Weight of Coated Tablet			103.000	206.000	412.000	100.000

(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)

R REGIONAL INFORMATION

Environmental

- Laurus Labs Limited states that for this Abbreviated New Drug Application (ANDA) we are subject to a categorical exclusion from the requirement to prepare an Environmental Assessment Statement, as per 21 CFR § 25.30, 25.31, 25.33 and 25.15 (d).
- This ANDA is for the drug product which will not be indicated for administration at a higher dose level, nor for a longer duration, or for different indications than those that are in effect. No extraordinary circumstances, as outlined in 21 CFR § 25.21, exist. Hence, a categorical exclusion from the requirement to prepare an Environmental Assessment is hereby requested.
- Also, Laurus Labs Limited, hereby states that we are in compliance with all federal, state and local environmental laws.

Assessment:
Adequate

Adequate

Methods Validation or Verification Package

Assessment:

Adequate

Comparability Protocols

Assessment:
N/A

Choose an item.

Lifecycle Management Considerations

DRUG PRODUCT LIST OF DEFICIENCIES

1.

2.

3.

4.

(b) (4)

(b) (4)

5.

6.

7.

(b) (4)

8.

9.

10.

11.

(b) (4)

CHAPTER III: ENVIRONMENTAL

[IQA ANDA Assessment Guide Reference](#)

R REGIONAL INFORMATION

Environmental

- Laurus Labs Limited states that for this Abbreviated New Drug Application (ANDA) we are subject to a categorical exclusion from the requirement to prepare an Environmental Assessment Statement, as per 21 CFR § 25.30, 25.31, 25.33 and 25.15 (d).
- This ANDA is for the drug product which will not be indicated for administration at a higher dose level, nor for a longer duration, or for different indications than those that are in effect. No extraordinary circumstances, as outlined in 21 CFR § 25.21, exist. Hence, a categorical exclusion from the requirement to prepare an Environmental Assessment is hereby requested.
- Also, Laurus Labs Limited, hereby states that we are in compliance with all federal, state and local environmental laws.

Assessment:
Adequate

Adequate

CHAPTER IV: LABELING

[IQA ANDA Assessment Guide Reference](#)

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	Dimension (mm) (Length x Width)	Imprint Code
24mg/26mg	9.11x 5.08	Violet white color, oval, biconvex film-coated tablets debossed with "S5" on one side and plain on the other side.
49mg/51mg	12.75 x 5.90	Pale yellow color, oval, biconvex film-coated tablets debossed with "S1" on one side and plain on the other side.
97mg/103mg	12.57 x 6.85	Light pink color, oval, biconvex film-coated tablets debossed with "S2" on one side and plain on the other side.

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

A. Drug Substance Deficiencies

None

B. Drug Product Deficiencies

None

C. Labeling Deficiencies

None

(END OF DRUG PRODUCT QUALITY ASSESSMENT)

Signature Block:

Primary DP Assessor: *Xihong Wang*

Date: 12/19/19;
3/31/2020;
1/22/2021
7/1/2021,
09/16/2021

Secondary DP Assessor: *Marco Bennett*

Date: 12/19/2019;
04.01.2020;
04.14.2020;
01.22.2021;
07.02.2021;
09.17.2021



Xihong
Wang

Digitally signed by Xihong Wang

Date: 9/17/2021 01:19:42PM

GUID: 508da7410002ba99af7b0597dc38d164



Marco A.
Bennett

Digitally signed by Marco A. Bennett

Date: 9/22/2021 06:38:50AM

GUID: 508da705000289bae41af5c5413d8455

MANUFACTURING INTEGRATED ASSESSMENT

Application ID	ANDA 213676
Drug Product Name	Sacubitril and Valsartan Tablets
Strengths	24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg
Dosage Form	Tablets
Administration Route	Oral
Indication	(b)(4)
Applicant Name	Laurus Labs Limited
RLD Number	207620

I. Manufacturing Summary

Facility Assessment Recommendation: Adequate

Process Assessment Recommendation: Adequate

Assessment Summary:

Sacubitril and Valsartan Tablets 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg is manufactured using (b)(4)

(b)(4)

The DS manufacturer, DP manufacturer, Critical Intermediate manufacturer and external testing facility are recommended for approval based on compliance history, acceptable profile codes and experience in the proposed responsibilities.

List Submissions being assessed (Table):

Document Description (SD #)	Date Received
Original (SD# 0001)	07/08/2019
Response to IR (SD# 0003)	09/16/2019
Response to IR (SD#0007)	02/06/2020
Response to IR (SD#0008)	03/02/2020
Response to CR (SD#0009)	07/01/2020

Highlight Key Issues from Last Cycle and Their Resolution: 1st Cycle

Review #1

(b)(4)

(b)(4)

Review #2

(b)(4)

Concise Description of Outstanding Issues (List bullet points with key information and update as needed):

- None

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
Laurus Labs Limited (b)(4) (b)(4) Plot No. 19, 20 and 21, Western Sector, APSEZ, Atchutapuram, Visakhapatnam, Andhra Pradesh, India, 531011	3011538548	(b)(4)	Approve - Based on Previous History
Laurus Labs Limited (b)(4) (b)(4) Plot No. 21, Jawaharlal Nehru Pharma City Parawada, Visakhapatnam, Andhra Pradesh, India, 531021	3007083664		Approve - Based on PAI
Laurus Labs Limited (b)(4) Plot No. 18, Jawaharlal Nehru Pharma City Parawada, Visakhapatnam, Andhra Pradesh, India, 531021	3007083664		Approve - Based on Previous History
(b)(4)			Approve - Based on PAI (In lieu of PAI, documents)

(b)(4)

assessed
using
704(a)(4)

(b)(4)

(b)(4)

Approve -
Based on
PAI
(In lieu of
PAI,
documents
assessed
using
704(a)(4))

(b)(4)

* Note Linhai Tianyu Pharmaceutical Co is already included in from 356h of the application.

II. Drug Product Manufacturing

1. Batch Formula

Comparative Quantitative Batch Formula Composition (Exhibit Batch vs Intended Commercial Batch)

The comparative batch formula of exhibit batches and intended commercial batches of Sacubitril and Valsartan Tablets 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg is presented in below table:

Ingredients	Quality Standard	Exhibit Batch Size (b)(4)		Intended Commercial Batch Size (b)(4)	
		Quantity per batch (kg)	Quantity per batch %(w/w)	Quantity per batch (kg)	Quantity per batch %(w/w)
Intra-granular Part					
Sacubitril-Valsartan 3Na Complex [‡]	In-House	(b)(4)			
Low-substituted hydroxypropylcellulose (b)(4)	USP-NF				
Microcrystalline Cellulose (b)(4)	USP-NF				
Crospovidone (b)(4)	USP-NF				
Silicon dioxide (b)(4)	USP-NF				
Magnesium Stearate (b)(4)	USP-NF				
		(b)(4)	100.00	(b)(4)	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)

V. List of Outstanding Information Request/Deficiencies:

Outstanding Deficiencies Collation Table
None

VI. Signature Block

Round#	Primary Name	Secondary & Other Names	Date of Completion	Assessment Outcome	Facility OMIR
1	Mesfin Abdi 11/12/2019	Jean Tang 12/04/2019	12/5/2019	IR	Withheld
2	Mesfin Abdi 02/13/2020	Jean Tang 02/19/2020	2/19/2020	IR	Withheld
3	Mesfin Abdi 03/03/2020 04/28/2020	Jean Tang 03/13/2020 04/29/2020	4/29/2020	Adequate	Withheld

4	Mesfin Abdi 12/18/2020	Jean Tang 12/23/2020	12/23/2020	Adequate	Approve

BIOPHARMACEUTICS ANDA REVIEW	
Application No.	ANDA-213676-ORIG-1
Applicant	Laurus Labs Limited
Product Name/ Strength(s)	Sacubitril and Valsartan Tablets/ 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg
Dosage Form/Route	Immediate-Release Tablets/Oral
Indication	Reduce the risk of cardiovascular death and hospitalization for heart failure
Submission Date(s)	7/8/2019 – Original Submission 2/6/2020 – Response to Information Request
RLD/RS	Entresto® Tablets [N207620]
Primary Reviewer	Churg Chan, Pharm.D.
Secondary Reviewer	Om Anand, Ph.D.
Recommendation	Adequate

EXECUTIVE SUMMARY:

This Biopharmaceutics Review evaluates data supporting the adequacy of the proposed dissolution method and acceptance criteria for quality control testing of the proposed drug product.

Dissolution Method:

(b)(4)

Based on the provided information and data, the proposed dissolution method (Table 1) is deemed adequate for quality control testing of the proposed product. The Applicant’s originally proposed dissolution acceptance criteria were (b)(4) and therefore not acceptable. Based on the provided data, the Applicant was recommended via an Information Request dated January 3, 2020 to revise the dissolution acceptance criteria to (b)(4)

(b)(4)

(b)(4)

In a response dated February 6, 2020, the Applicant accepted the FDA recommendation regarding the dissolution acceptance criterion for the 49 mg/51 mg and 97 mg/103 mg strengths, however, they proposed “NLT ^{(b)(4)} % (Q) of Sacubitril and Valsartan in 30 minutes” for the 24 mg/26 mg strength as well. Based on the totality of the information/data submitted, the newly proposed dissolution acceptance criterion and the response is acceptable.

¹ [FDA Recommended Dissolution Methods](#)

Table 1. Approved dissolution method and acceptance criteria²

Method Source	USP Apparatus	Speed	Medium	Volume/ Temperature	Recommended Acceptance Criteria
FDA – Database	II (Paddle)	50 RPM	pH 6.8 Phosphate Buffer	900 mL/ 37 ± 0.5°C	NLT $\frac{Q}{Q_0}$ % (Q) of Sacubitril in 30 minutes NLT $\frac{Q}{Q_0}$ % (Q) of Valsartan in 30 minutes

Recommendation:

From a Biopharmaceutics perspective, ANDA 213676 for the proposed Sacubitril/Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg, is recommended for **approval**.

² [Application 213676 - Sequence 0001 - Pharmaceutical Development Report](#)

BIOPHARMACEUTICS REVIEW

1. **Drug Substance Solubility:** (b)(4)
(b)(4)
2. **Formulation:** The proposed product is (b)(4)
(b)(4)
3. **Bioequivalence:** The Applicant performed *in vivo* pharmacokinetic studies using the 97 mg/103 mg strength of the proposed and RLD products in both fasting and fed conditions.⁶ Under fasting conditions, the T_{max} of Sacubitril and Valsartan were 0.71 and 2.14 hours, respectively.⁷ Under fed conditions, the T_{max} of Sacubitril and Valsartan were 1.83 hours and 3.31 hours, respectively.⁸ The Division of Bioequivalence/OGD will evaluate the bioequivalence study results and the biowaiver request.
4. **Dissolution Method:** The Applicant proposes to use the same dissolution method for Sacubitril/Valsartan tablets as previously described in the FDA's dissolution database (Table 1).⁹

The Applicant evaluated discriminating ability of the proposed dissolution method on changes of high-risk formulation variables (b)(4)

(b)(4)

(b)(4) The dissolution profiles were similar across the formulations evaluated with the proposed dissolution method. However, based on the totality of the provided data and information, the proposed dissolution method is deemed adequate for quality control testing of the proposed product.

In an Information Request dated January 3, 2020, the Applicant was asked to submit dissolution data using the new dissolution method described in the FDA's dissolution database

³ [Application 213676 - Sequence 0001 - Quality Overall Summary - Drug Substance \(PDF\)](#)

⁴ [Application 213676 - Sequence 0001 - Description of Manufacturing Process and Process Controls](#)

⁵ [Application 213676 - Sequence 0001 - Description and Composition of the Drug Product](#)

⁶ [Application 213676 - Sequence 0001 - Tabular Listing of All Clinical Studies \(Pivotal Batch\)](#)

⁷ [Application 213676 - Sequence 0001 - Clinical Study Report Body - Fasting Study](#)

⁸ [Application 213676 - Sequence 0001 - Clinical Study Report Body - Fed Study](#)

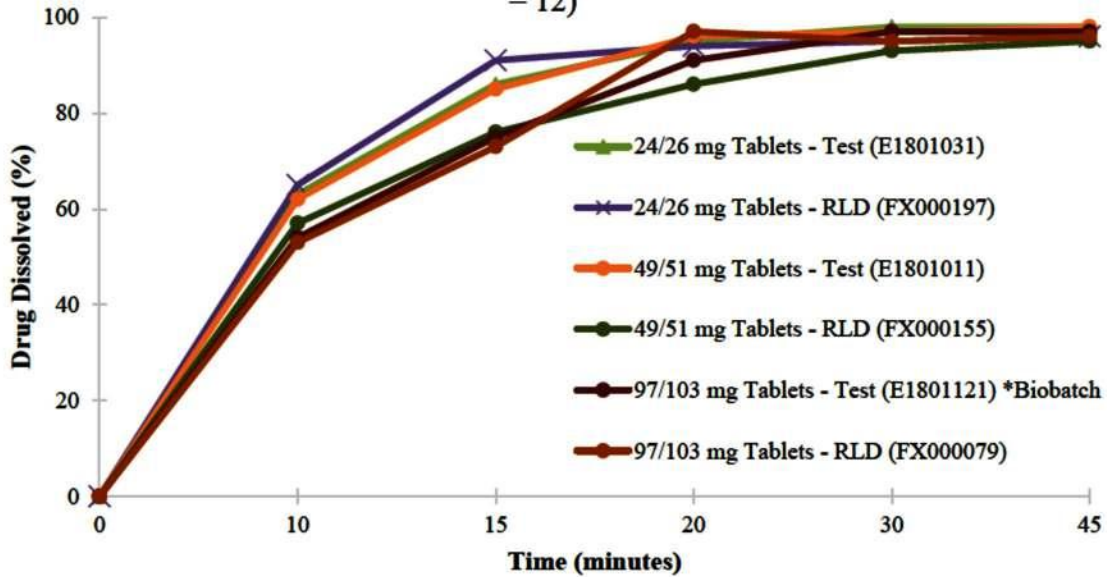
(b)(4)

(b)(4)

The dissolution data generated from this new dissolution method show dissimilarity between the biobatch and the exhibit batches ($f_2 < 50$). The Applicant proposed to continue using their original dissolution method for their proposed drug product [900 mL of pH 6.8 phosphate buffer using USP Apparatus II (Paddle) at 50 rpm].

5. Dissolution Data:¹¹

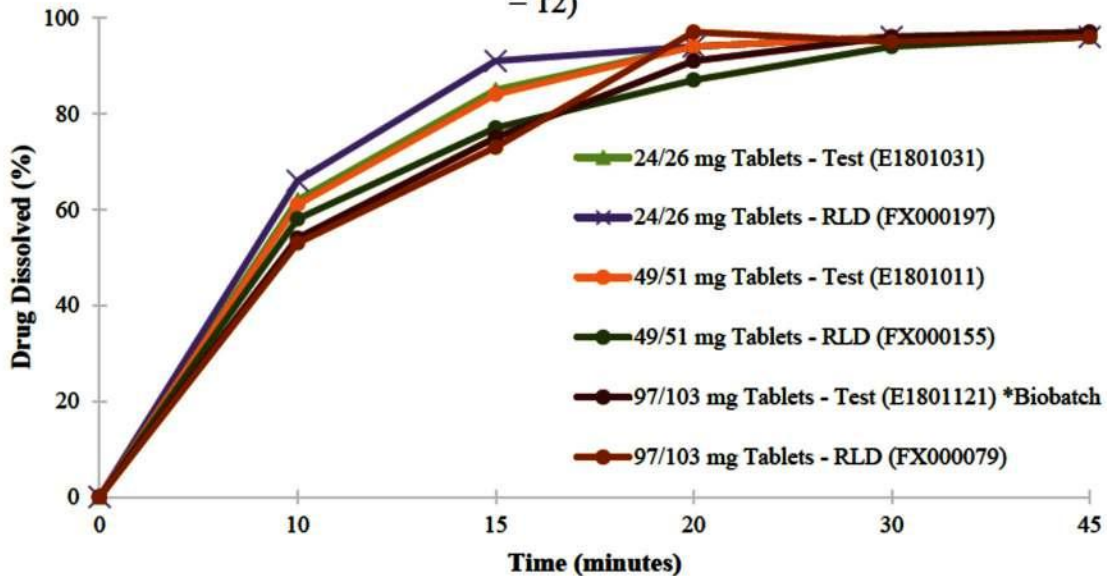
Figure 1. Summary of mean *in vitro* dissolution data for Sacubitril ($n = 12$)



¹⁰ [Application 213676 - Sequence 0007 - Comparative In-Vitro Dissolution Data](#)

¹¹ [Application 213676 - Sequence 0001 - Clinical Summary \(PDF\)](#)

Figure 2. Summary of mean *in vitro* dissolution data for Valsartan (*n* = 12)



6. **Dissolution Acceptance Criteria:** The original dissolution acceptance criteria proposed by the Applicant, (b)(4) not supported by the data. The Applicant was recommended via an Information Request dated January 3, 2020 to implement the dissolution acceptance criteria of (b)(4)

(b)(4)

(b)(4) In a response dated February 6, 2020, the Applicant accepted the FDA recommendation regarding the dissolution acceptance criterion for the 49 mg/51 mg and 97 mg/103 mg strengths, however, they proposed “NLT (b)(4) % (Q) of Sacubitril and Valsartan in 30 minutes” for the 24 mg/26 mg strength as well. The Applicant justified their proposition by reviewing data at (b)(4) 30 minutes for all their exhibit batches and the RLD. Both the proposed and reference drug product have individual unit values (b)(4) % at the (b)(4) (b)(4) time point, but this trend was not observed at the 30-minute time point. Therefore, based on the totality of the provided data and information, the Applicant’s proposed acceptance criteria are acceptable.

7. **Stability:** The Applicant provided stability data for exhibit batches of Sacubitril and Valsartan tablets for 6 months under long-term ($25^{\circ} \pm 2^{\circ}\text{C}/60\% \pm 5\% \text{RH}$) and accelerated ($40^{\circ} \pm 2^{\circ}\text{C}/75\% \pm 5\% \text{RH}$) conditions.¹² No significant changes in dissolution in stability were observed using the proposed dissolution method.
8. **Dissolution Risk/Mitigation Assessment:** The biopharmaceutics and dissolution risk are relatively high because Sacubitril and Valsartan are considered (b)(4) per the

¹² [Application 213676 - Sequence 0001 - Stability Summary and Conclusion](#)

Applicant's BCS claims. The dissolution acceptance criteria are adequately selected to mitigate the risk of dissolution failure for the proposed drug product.

Biopharmaceutics Information Request

The following *Biopharmaceutics Information Request (IR)* comments were conveyed to the Applicant on January 3, 2020:

1. Based on the provided information and data, the proposed dissolution method (USP II at 50 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 (b)(4) dissolution acceptance criteria and therefore the proposed acceptance criterion is not acceptable. Implement the following acceptance criteria for your proposed product, Sacubitril and Valsartan Tablets:

(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.

2.

(b)(4)

(b)(4) Please submit dissolution data [(N=12, individual, mean, CV%)] for the bio-batch and at least one batch of other strengths using this new dissolution method. (b)(4)

(b)(4)

The Applicant responded to the above *Biopharmaceutics Information Request (IR)* on February 6, 2020 and accepted the recommended dissolution acceptance criteria of $Q = (b)(4)\%$ at 30 minutes for the 49 mg/51 mg and 97 mg/103 mg strengths. The Applicant also proposed the same dissolution acceptance criterion of $Q = (b)(4)\%$ at 30 minutes for their 24 mg/26 mg strength. The Applicant provided dissolution data using the new FDA dissolution database method, however, they proposed to continue using their originally proposed dissolution method. Given the available data, the response is acceptable.



Churg
Chan

Digitally signed by Churg Chan
Date: 2/28/2020 07:37:19AM
GUID: 5d7a585a001ef2629ce8f26f9631f545



Om
Anand

Digitally signed by Om Anand
Date: 2/28/2020 10:00:25AM
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Marco A.
Bennett

Digitally signed by Marco A. Bennett

Date: 9/22/2021 03:17:37PM

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**U.S. FOOD & DRUG
ADMINISTRATION**

DRUG PRODUCT QUALITY ASSESSMENT

ANDA 213676 (Review Cycle # 03)

Sacubitril and Valsartan Tablets,

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

Xihong Wang

Division of Immediate Release Products I/Branch II

Office of Lifecycle Drug Products

Office of Pharmaceutical Quality

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ANDA 213676 (Assessment Cycle # 03)

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	Laurus Labs Limited Second Floor, Serene Chambers, Road No.7, Banjara Hills Hyderabad, Telangana India, 500034
Drug Product Manufacturer	(b) (4)
US agent, if applicable	☐ N/A ☒ (See Below) Sharath Koripally, Senior Director RA, QA & PV Laurus Generics Inc. 400 Connell Drive, Suite 5200 Berkeley Heights, NJ 07922 Tel: (718) 510-6822 Email: sharath.koripally@laurusgenerics.com
Proposed Indication	(b) (4)

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original (Subject of review #1)	07/08/2019	All
Amendment: Response to DRL-Labeling dated 10/25/19 (Subject of review #1)	11/07/2019	Labeling
Amendment: Response to DRL-Labeling dated 01/03/20 (Subject of review #1, IR#1)	02/06/2020	DP, Biopharm, Process
Amendment: Response to IR letter from the agency (Biopharm) dated 02/20/2020 (Subject of Biopharm review)	03/02/2020	Biopharm
Amendment: Response to CR letter from the agency dated 05/04/2020 (Subject of review #2)	07/01/2020	DP, Facility, BE
Amendment: Response to CR letter from the agency dated 02/22/2021 (Subject of review #3)	05/03/2021	DP, Labeling
General Correspondence: Change in US agent (Updated in the table above)	08/02/2021	

QUALITY ASSESMENT DATA SHEET

[IQA ANDA Assessment Guide Reference](#)

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Reviewed	Comments
33647	II	Laurus Labs Limited	Sacubitril-Valsartan 3Na Complex	Adequate	09/16/2021	Xianru Sun
Other DMF: ☐ N/A ☒ (See Below)						
(b)(4)	III	(b)(4)	(b)(4)			
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	IV					

(b)(4)

B. OTHER DOCUMENTS: IND, RLD, RS, Approved ANDA

Document	Application Number	Brand Name	Description
NDA (RLD)	NDA 207620	ENTRESTO® (sacubitril and valsartan) tablets	ENTRESTO® (sacubitril and valsartan) tablets 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg, manufactured by Novartis Pharmaceuticals Corporation. Approval date: 07/07/2015

2. CONSULTS: None

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology				
CDRH-ODE				
CDRH-OC				
Clinical				
Other				

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

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CHAPTER I: DRUG SUBSTANCE

[IQA ANDA Assessment Guide Reference](#)

Drug Substance Name	Sacubitril-Valsartan 3Na Complex
DMF Number (If Applicable)	033647
DMF Status	Inadequate - Major
DMF Holder	Laurus Labs Limited

Overall Assessment Recommendation for DS:

DRL

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.

Highlight Key Issues from Last Cycle and Their Resolution:

N/A - This is the review of original ANDA

Concise Description of Outstanding Issues:

Choose an item.

Select Number of Approved Comparability Protocols: 0

S.1 GENERAL INFORMATION

Nomenclature/Chemical name	: Tri sodium [3-((1 <i>S</i> ,3 <i>R</i>)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl -1-butylcarbamoyl)propionate-(<i>S</i>)-3'-methyl-2'-(pentanoyl {2''-(tetrazol-5-ylate) biphenyl-4'-ylmethyl} amino)butyrate]				
	(or) Tri sodium (4-[[[(1 <i>S</i> ,3 <i>R</i>)-1-([1,1'-biphenyl-4-ylmethyl-4-ethoxy-3-methyl-4-oxobutyl]amino)-4-oxobutanoate)(N-pentanoyl-N-{2'-(1 <i>H</i> -tetrazol-1-id-5-yl) [1,1'-biphenyl]-4-yl]methyl}-L-valinate)				
	<table border="1"> <thead> <tr> <th>Sacubitril</th> <th>Valsartan</th> </tr> </thead> <tbody> <tr> <td>4-[[[(1<i>S</i>,3<i>R</i>)-1-([1,1'-Biphenyl] -4-ylmethyl)-4-ethoxy -3-methyl-4-oxobutyl]amino]-4-oxobutanoic acid</td> <td>N-Pentanoyl-N-{[2'-(1<i>H</i>-tetrazol-5-yl)[1,1'-biphenyl] -4-yl]methyl}-L-valine</td> </tr> </tbody> </table>	Sacubitril	Valsartan	4-[[[(1 <i>S</i> ,3 <i>R</i>)-1-([1,1'-Biphenyl] -4-ylmethyl)-4-ethoxy -3-methyl-4-oxobutyl]amino]-4-oxobutanoic acid	N-Pentanoyl-N-{[2'-(1 <i>H</i> -tetrazol-5-yl)[1,1'-biphenyl] -4-yl]methyl}-L-valine
Sacubitril	Valsartan				
4-[[[(1 <i>S</i> ,3 <i>R</i>)-1-([1,1'-Biphenyl] -4-ylmethyl)-4-ethoxy -3-methyl-4-oxobutyl]amino]-4-oxobutanoic acid	N-Pentanoyl-N-{[2'-(1 <i>H</i> -tetrazol-5-yl)[1,1'-biphenyl] -4-yl]methyl}-L-valine				
International Non-proprietary Name (INN)	: Not reported				
Compendial Name (WHO)	: Not reported				
United States Adopted Name (USAN)	: Sacubitril and valsartan				
Molecular Structure	: Sacubitril-Valsartan 3Na Complex				
Molecular Formula	: C ₄₈ H ₅₅ N ₆ O ₈ .3Na				
CAS number	: 936623-90-4				
Relative Molecular mass	: 912.95				
Pharmacological Class	: Angiotensin II receptor and neprilysin inhibitor for the treatment of chronic heart failure (NYHA Class II-IV) and reduced ejection fraction.				

Physical form	: White to off-white solid
	(b)(4)

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Assessment:

Adequate

(b) (4)

Assessment:
N/A

Choose an item.

R REGIONAL INFORMATION

Comparability Protocols N/A (See Below)

Assessment:

Choose an item.

Lifecycle Management Considerations

DRUG SUBSTANCE LIST OF DEFICIENCIES:

- 1.
- 2.
- 3.
- 4.

(b) (4)

CHAPTER II: DRUG PRODUCT

[IQA ANDA Assessment Guide Reference](#)

Overall Assessment Recommendation: **Discipline Review Letter (DRL)**

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:

Drug Product CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Review Cycle #2	Comments*
Physical stability (solid state)	36 Medium	(b)(4)	Low	(b)(4)
Chemical Stability	48 Medium		Low	
Assay	18 Low		Low	
Content uniformity	24 Low			

		(b)(4)		(b)(4)
Microbial limits	9 Low		Low	
Dissolution	48 Medium			

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 the 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. Biopharm review is inadequate.*
- *Elemental impurity compliance with ICH Q3D – status: Adequate*
- *Number of Comparability protocols included: 0*

RLD versus Generic Product – NOT FOR FOIA

(b) (4)

* For repacking purpose only

P.1 DESCRIPTION AND COMPOSITION

Component/Composition of Sacubitril and Valsartan Tablets 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg

Ingredients	Compendial Reference	Pharmaceutical Function	24mg/26mg	49mg/51mg	97mg/103mg	%w/w
			(mg/ Tablet)			
Intra-granular materials						
Sacubitril-Valsartan 3Na Complex [^]	In-House	Active Ingredient	(b)(4)			
Low-substituted hydroxypropylcellulose (b)(4)	USP-NF	(b)(4)				
Microcrystalline Cellulose (b)(4)	USP-NF					
Crospovidone (b)(4)	USP-NF					
(b)(4)	USP-NF					
Silicon dioxide (b)(4)	USP-NF					
(b)(4)	USP-NF					
Magnesium Stearate (b)(4)	USP-NF					
(b)(4)						
Weight of Coated Tablet			103.000	206.000	412.000	100.000

(b)(4)

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(b)(4)

Assessment:

Inadequate

(b)(4)

R REGIONAL INFORMATION

Environmental

- Laurus Labs Limited states that for this Abbreviated New Drug Application (ANDA) we are subject to a categorical exclusion from the requirement to prepare an Environmental Assessment Statement, as per 21 CFR § 25.30, 25.31, 25.33 and 25.15 (d).
- This ANDA is for the drug product which will not be indicated for administration at a higher dose level, nor for a longer duration, or for different indications than those that are in effect. No extraordinary circumstances, as outlined in 21 CFR § 25.21, exist. Hence, a categorical exclusion from the requirement to prepare an Environmental Assessment is hereby requested.
- Also, Laurus Labs Limited, hereby states that we are in compliance with all federal, state and local environmental laws.

Assessment:

Adequate

Adequate

Methods Validation or Verification Package

Assessment:

Adequate

Comparability Protocols

Assessment:

Choose an item.

N/A

Lifecycle Management Considerations

DRUG PRODUCT LIST OF DEFICIENCIES

1.

2.

3.

4.

(b) (4)

(b) (4)

5.

6.

7.

(b) (4)

8.

9.

10.

11.

(b) (4)

CHAPTER III: ENVIRONMENTAL

[IQA ANDA Assessment Guide Reference](#)

R REGIONAL INFORMATION

Environmental

- Laurus Labs Limited states that for this Abbreviated New Drug Application (ANDA) we are subject to a categorical exclusion from the requirement to prepare an Environmental Assessment Statement, as per 21 CFR § 25.30, 25.31, 25.33 and 25.15 (d).
- This ANDA is for the drug product which will not be indicated for administration at a higher dose level, nor for a longer duration, or for different indications than those that are in effect. No extraordinary circumstances, as outlined in 21 CFR § 25.21, exist. Hence, a categorical exclusion from the requirement to prepare an Environmental Assessment is hereby requested.
- Also, Laurus Labs Limited, hereby states that we are in compliance with all federal, state and local environmental laws.

Assessment:
Adequate

Adequate

CHAPTER IV: LABELING

[IQA ANDA Assessment Guide Reference](#)

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	Dimension (mm) (Length x Width)	Imprint Code
24mg/26mg	9.11x 5.08	Violet white color, oval, biconvex film-coated tablets debossed with "S5" on one side and plain on the other side.
49mg/51mg	12.75 x 5.90	Pale yellow color, oval, biconvex film-coated tablets debossed with "S1" on one side and plain on the other side.
97mg/103mg	12.57 x 6.85	Light pink color, oval, biconvex film-coated tablets debossed with "S2" on one side and plain on the other side.

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

A. Drug Substance Deficiencies

None

B. Drug Product Deficiencies

None

C. Labeling Deficiencies

None

(END OF DRUG PRODUCT QUALITY ASSESSMENT)

Signature Block:

Primary DP Assessor: *Xihong Wang*

Date: *12/19/19;
3/31/2020;
1/22/2021
7/1/2021,
09/16/2021*

Secondary DP Assessor: *Marco Bennett*

Date: *12/19/2019;
04.01.2020;
04.14.2020;
01.22.2021;
07.02.2021;
09.17.2021*



Xihong
Wang

Digitally signed by Xihong Wang

Date: 9/17/2021 01:19:42PM

GUID: 508da7410002ba99af7b0597dc38d164



Marco A.
Bennett

Digitally signed by Marco A. Bennett

Date: 9/22/2021 06:38:50AM

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RECOMMENDATION

☐ Complete Response-Minor
☒ Complete Response-Major
☐ Complete Response-Major-Facilities Only

CR-Major DMF Justification:

Inadequate selection or justification of starting materials: Submission of additional information or new batch is needed. Upon receipt, the review of this information will require substantial expenditure of FDA resources.

(b)(4) **New**
toxicology studies are requested (b)(4) 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.

(b)(4)
(b)(4) **Submission of additional**
information is needed. Upon receipt, this information will require thorough evaluation and will potentially affects other aspects of the application and the related conclusions.

ANDA 213676 Assessment #2

Drug Product Name	Sacubitril and Valsartan Tablets Capsules
Dosage Form	Capsules
Strength	24mg/26mg, 49mg/51mg and 97mg/103mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Laurus Labs Limited
US agent, if applicable	PharmaQ, Inc.

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original/Initial Submission	07/08/2019	Quality
Amendment Correspondence/Amendment Verification Statement - Quality/Response To Information Request	09/16/2019	Quality
Amendment Correspondence/Amendment Verification Statement; Quality/Response to Discipline Review Letter	02/06/2020	Quality
Quality/Response To Information Request; Amendment Correspondence/Amendment Verification Statement	03/02/2020	Quality
Resubmission/After Action- Complete; Amendment Correspondence/Amendment Verification Statement; Bioequivalence/Other; Quality/Quality Information; Quality/Facility Information	07/01/2020	Quality

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Master File	Xihong Wang	Marco A. Bennett
Drug Product	Xihong Wang	Marco A. Bennett
Facility	Mesfin Abdi	Jean Tang
Biopharmaceutics	Churg Chan	Om Anand
Regulatory Business Process Manager	Kevin Ninan	
Application Technical Lead	Marco A. Bennett	
Laboratory (OTR)		
Environmental		

QUALITY ASSESMENT DATA SHEET

[IQA ANDA Assessment Guide Reference](#)

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Reviewed	Comments
33647	II	Laurus Labs Limited	Sacubitril-Valsartan 3Na Complex	Inadequate -Major	12/18/2019	Xianru Sun
Other DMF: ☐ N/A ☒ (See Below)						
(b)(4)	III	(b)(4)	(b)(4)			
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					

(b)(4)	III	(b)(4)			
	IV				

ABBREVIATED EXECUTIVE SUMMARY (CR ONLY)

[IQA ANDA Assessment Guide Reference](#)

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Major

The OPQ action is a CR-Major owing to DP assessment being a Major.

II. QUALITY ASSESSMENT OVERVIEW

A. Drug Substance: Inadequate-Major

1. Primary Justification:

CR-Major DMF Justification:

Inadequate selection or justification of starting materials: Submission of additional information or new batch is needed. Upon receipt, the review of this information will require substantial expenditure of FDA resources.

(b)(4)

New toxicology studies are requested (b)(4) 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.

(b) (4)

2. Secondary Justification (if necessary):

None

3. Tertiary Justification (if necessary):

None

4. Insert additional justification below (if necessary)

None

The Drug Substance assessment is inadequate owing to the DMF being inadequate.

Drug Product: Inadequate-Minor

1. Primary Justification:

None

2. Secondary Justification (if necessary):

None

3. Tertiary Justification (if necessary):

None

4. Insert additional justification below (if necessary)

None

The Drug Product assessment is inadequate.

Labeling: Adequate

The OPQ Labeling assessment is adequate.

B. Manufacturing: Adequate

1. Primary Justification:

None

2. Secondary Justification (if necessary)

None

3. Tertiary Justification (if necessary):

None

4. Insert additional justification below (if necessary)

None

The Manufacturing assessment is adequate.

C. Biopharmaceutics: Adequate

1. Primary Justification:

None

2. Secondary Justification (if necessary):

None

3. Tertiary Justification (if necessary):

None

4. Insert additional justification below (if necessary)

None

The Biopharmaceutics assessment is adequate.

D. Microbiology: Choose an item. 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.

2.

(b) (4)

3. **Drug Product Deficiencies**

1. Please provide all accrued room temperature stability data in your next amendment.

4. **Labeling Deficiencies (Please contact OGD if you identify any Labeling deficiencies with your comments):** None

5. **Manufacturing Deficiencies:** None

6. **Biopharmaceutics Deficiencies:** None

7. **Microbiology Deficiencies:** None

8. **Other Deficiencies (Specify discipline, such as Environmental):**
None

Application Technical Lead Name and Date: Marco A. Bennett, 02.11.2021



Marco A.
Bennett

Digitally signed by Marco A. Bennett

Date: 2/11/2021 01:00:16PM

GUID: 508da705000289bae41af5c5413d8455



**U.S. FOOD & DRUG
ADMINISTRATION**

DRUG PRODUCT QUALITY ASSESSMENT

ANDA 213676 (Review Cycle # 02)

Sacubitril and Valsartan Tablets,

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

Xihong Wang

Division of Immediate Release Products I/Branch II

Office of Lifecycle Drug Products

Office of Pharmaceutical Quality

CR-Major DMF Justification:

Inadequate selection or justification of starting materials: Submission of additional information or new batch is needed. Upon receipt, the review of this information will require substantial expenditure of FDA resources.

(b)(4)

(b)(4)

New toxicology studies are requested

(b)(4)

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.

(b)(4)

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ANDA 213676 (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	Laurus Labs Limited Second Floor, Serene Chambers, Road No.7, Banjara Hills Hyderabad, Telangana India, 500034
Drug Product Manufacturer	(b)(4)
US agent, if applicable	☐ N/A ☒ (See Below) Dr. Jose D. Gomes, Ph.D., President, PharmaQ, Inc. Waterview Plaza, 2001 Route 46, Suite 105 Parsippany, NJ 07054 Tel: +(1)-973-402-5300 Fax: +(1)-973-368-1145 Email: jgomes@pharmaq.net
Proposed Indication	(b)(4)

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original (Subject of review #1)	07/08/2019	All
Amendment: Response to DRL-Labeling dated 10/25/19 (Subject of review #1)	11/07/2019	Labeling
Amendment: Response to DRL-Labeling dated 01/03/20 (Subject of review #1, IR#1)	02/06/2020	DP, Biopharm, Process
Amendment: Response to IR letter from the agency (Biopharm) dated 02/20/2020 (Subject of Biopharm review)	03/02/2020	Biopharm
Amendment: Response to CR letter from the agency dated 05/04/2020 (Subject of review #2)	07/01/2020	DP, Facility, BE

QUALITY ASSESMENT DATA SHEET

[IQA ANDA Assessment Guide Reference](#)

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Reviewed	Comments
33647	II	Laurus Labs Limited	Sacubitril-Valsartan 3Na Complex	Inadequate-Major	12/18/2019*	Xianru Sun
Other DMF: ☐ N/A ☒ (See Below)						
(b)(4)	III	(b)(4)	(b)(4)			
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	IV					

			(b)(4)			

*Amendment dated 05/15/2020 is pending for review.

B. OTHER DOCUMENTS: IND, RLD, RS, Approved ANDA

Document	Application Number	Brand Name	Description
NDA (RLD)	NDA 207620	ENTRESTO® (sacubitril and valsartan) tablets	ENTRESTO® (sacubitril and valsartan) tablets 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg, manufactured by Novartis Pharmaceuticals Corporation. Approval date: 07/07/2015

2. CONSULTS: None

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology				
CDRH-ODE				
CDRH-OC				
Clinical				
Other				

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.

Summary of Firm's Response:

Satisfactory

As requested by the agency, the specification of Crespovidone (Type-A) has been revised to include the microbiological quality test as retest parameter. Also, retest period has been revised from "2 years" to "1 year". The revised specification is provided in the Section 3.2.P.4.1 (Crespovidone) of this submission.

Also, we would like to inform to the Agency that the other excipients have already microbiological quality test as a retest parameter and retest period is one year.

Reviewer's Conclusion:

The firm added the microbiological quality test as retest parameter to Crespovidone and revised the retest period to 1 year. The other excipients have already microbiological quality test as a retest parameter and retest period is one year. The firm's response is satisfactory.

The information in P.4 control of excipients of this review has been updated.

Deficiency 2: Based on the information you have provided in the application for the assay of the bio batch used in support of the bioequivalence study and product release, we recommend that you revise your proposed release and stability criteria for assay for the production batches to be within 5% of the label claim to provide assurance that your product assay post approval would be comparable to the exhibit batch used to support the bioequivalence.

Summary of Firm's Response:

Not Satisfactory

As recommended by the agency, the assay limit of the release specification of drug product has been revised within 5% of the label claim.

However, the limits for the shelf-life specification has been tightened to keep within 7.5% of the label claim. The existing and proposed assay limits of the release and shelf-life specifications are tabulated below:

Test	Release Specification		Shelf-life Specification	
	Existing	Proposed	Existing	Proposed
Assay by HPLC (%w/w)				
Sacubitril	93.0 – 107.0 %	95.0 – 105.0 %	90.0 – 110.0 %	92.5 – 107.5 %
Valsartan	93.0 – 107.0 %	95.0 – 105.0 %	90.0 – 110.0 %	92.5 – 107.5 %

Additionally, the in-process specification has been revised to tighten the blend assay limits to have better control for the finished product. The existing and proposed limits in the in-process specifications are tabulated below:

Test	Blend Assay specification	
	Existing	Proposed
Sacubitril	93.0 – 107.0 %	95.0 – 105.0 %
Valsartan	93.0 – 107.0 %	95.0 – 105.0 %

Reviewer's Conclusion:

The firm tightened the assay limits to 95.0-105.0% (Release) and 92.5-107.5% (Stability). It is acceptable for release while not acceptable for stability as per the information available to the agency. **The firm will be asked to further tighten the stability specification.**

Informed the process and facility reviewer (Mesfin Abdi) by email about the revision of in-process specification on 2/18/2020.

New deficiency in review #1, IR#1:

Please further tighten the assay limit for the drug product stability specification to be within 5% of the label claim.

Deficiency 3: Your proposed acceptance criteria for Total Impurities in your drug product release and stability specifications are not satisfactorily justified. Please revise the specifications based on your PD study and batch experience or justify them by comparison with RLD results acquired using the same method of analysis.

Summary of Firm's Response:

Not Satisfactory

As recommended by the Agency, the limits for total impurities in release and stability specifications have been tightened further. The revised limit is based upon batch experience and in-line with "MAPP 5017.2: Establishing Impurity Acceptance Criteria" recommendation.

The existing and proposed limits in the release and shelf-life specifications are tabulated below:

Test	Release Specification		Shelf-life Specification	
	Existing	Proposed	Existing	Proposed
Total impurity limit (% w/w)	NMT 1.0	NMT 0.8	NMT 1.0	NMT 0.8

Reviewer's Conclusion:

The firm tightened the limits for total impurities from NMT 1.0% to NMT 0.8% (Release/Stability), which is not acceptable as per the information available to the agency. As per the available 6 months stability data at ACC and 12 months long term stability data, the maximum content of the total impurity is 0.2%. **The firm will be asked to further tighten the same based on the stability data.**

New deficiency in review #1, IR#1:

The total impurity specification is much higher than the actually observed impurity results. Please further tightened the limit for total Impurities in your drug product release and stability specifications based upon the batch experience or justify them by comparison with RLD results acquired using the same method of analysis.

Deficiency 4: Nitrosamines including N-Nitrosodimethylamine (NDMA) are potent genotoxic carcinogens. The drug product contains Valsartan and due to the agency’s on-going concern with presence of nitrosamines including NDMA in Valsartan and other ARB drug products, we recommend you have a validated analytical method to detect and quantitate nitrosamines including NDMA in your drug product.

You may use the published FDA methods (see reference below) for detecting and quantifying NDMA and other nitrosamines or use a fully validated in-house method that is equally or more sensitive than the published FDA methods. If you choose to use an in-house method, please provide a onetime method comparability study with the FDA published combined headspace method using samples spiked at the LOD for each impurity to demonstrate your method is suitable for use.

FDA’s published methods can be accessed at:
<https://www.fda.gov/drugs/drugsafety/ucm613916.htm>

Please provide us complete validation data and batch analyses data to demonstrate that your validated analytical method can detect and quantitate nitrosamines including NDMA in your drug product.

Summary of Firm’s Response:

Satisfactory

We acknowledge the agency’s comment.

We would like to inform the agency that we have carried out risk assessments on the formation of N-Nitrosamines including NDMA in Sacubitril/Valsartan Tablets. The NDMA and NDEA are routinely controlled in the Sacubitril-Valsartan 3Na complex with compound specific limits. Every batch of this drug substance that goes as an in-put starting material (Sacubitril-Valsartan 3Na Complex) for the drug product manufacturing is tested for NDMA and NDEA.

The results for NDMA and NDEA impurities in Sacubitril-Valsartan complex are provided below;

Table: Results of NDMA and NDMA impurities in the Sacubitril-Valsartan 3Na Complex

API Batch Number used in the manufacturing of exhibit batches of Sacubitril/Valsartan Tablets	Nitrosamines impurities results	
	NDMA (LOQ 0.01 ppm)	NDEA (LOQ 0.01 ppm)
ASVTCVSP10101118	Not detected	Not detected
ASVTCVSP10111118	Not detected	Not detected
ASVTCVSP10031118(PL)	Not detected	BDL
ASVTCVSP10041118(PL)	Not detected	BDL
ASVTCVSP10051118(PL)	Not detected	BDL

The “nitrosamine-related” risk assessment report including the excipients vendors’ declaration for the absences of nitrosamines is provided as an **Annexure 2** of this submission.

Considering the NDMA and NDEA impurity analysis in the starting material (Sacubitril-Valsartan 3Na Complex), manufacturing process of the drug product including inactive ingredients, solvents used in manufacturing of tablets and its vendors declaration for drugs substance, excipients and packaging material, Laurus Labs confirms that occurrence of N-Nitrosamines N-Nitrosodimethylamine (NDMA), N-Nitrosodiethylamine (NDEA), N-Nitrosodiisopropylamine (NDIPA), N-Nitrosoethylisopropylamine (NEIPA), N-Nitroso-N-methyl-4-aminobutyric acid (NMBA) and N-Nitrosodibutylamine (NDBA) in the drug product is not possible. Hence, the detection and quantitation of nitrosamines including NDMA in drug product is not deemed necessary.

Reviewer's Conclusion:

The firm provided risk assessment for the potential formation of Nitrosamines in Sacubitril-Valsartan Tablets. This risk assessment evaluated all the factors involved during the manufacturing of Sacubitril/Valsartan Tablets (the drug substance Sacubitril-Valsartan 3Na complex, inactive substances used in the manufacturing process of the drug product and cGMP considerations).

1. Assessment of N-nitrosamine impurities formation in the drug substance (Sacubitril-Valsartan 3Na complex) used in the drug product:

Based on the synthetic route, the formation of N-nitrosamines is not possible in the synthesis of Sacubitril sodium. There is a remote possibility of contamination of N-nitrosamines, especially NDMA, in Valsartan depending upon the reagents used for the tetrazole ring formation during the synthesis of Valsartan. The controls for the 5 nitrosamines i.e., NDMA, NDIPA, NEIPA, NMBA, and NDBA has been controlled in Valsartan. NDMA and NDEA are also routinely controlled in the Sacubitril-Valsartan 3Na complex with compound specific limits. The DS (Sacubitril-Valsartan 3Na complex) used for manufacturing the DP is tested for NDMA and NDEA and they are below the detection limit or not detected. It can be concluded that there is no risk of carryover of any nitrosamine from Sacubitril-Valsartan 3Na to the drug product.

2. Assessment of inactive substances used in the manufacturing of drug product:

- The vendors of all the excipients used in the drug product manufacturing have confirmed the absence of nitrosamine in their finished pharmaceutical excipient.
- There is no possibility of introduction of nitrosamine impurities from these solvents.
- The packaging materials used in drug product were evaluated for Nitrosamines and the vendors of all the packaging material have confirmed the absence of nitrosamine in their packaging materials.

3. Assessment of the manufacturing process of drug product with regards to cGMP:

The manufacturing of the drug product is performed under cGMP conditions using a validated process. The cleaning procedures for the equipment are validated for other sartans or compounds likely to be contaminated with nitrosamines are manufactured in this equipment. Hence, there is no potential for any cross contamination of the nitrosamines from other products.

Considering the manufacturing process of the drug product, its starting material and inactive substance, and the cGMP aspects, the occurrence of N-Nitrosamines NDMA, NDEA, NDIPA, NEIPA, NMBA and NDBA in the drug product is not possible. Hence, the detection and quantitation of nitrosamines including NDMA in drug product is not deemed necessary. The firm's response is satisfactory.

Deficiency 5: Please clarify which laboratory developed and validated the HPLC method for the drug product assay.

Summary of Firm's Response:

Satisfactory

We would like to clarify to the Agency that the Assay method by HPLC was developed and validated at our R&D site and successfully transferred to the manufacturing site, Laurus Labs Limited, (VSP-2).

The detailed information regarding originating as well as receiving site is presented below.

Originating Site	Receiving Site
Laurus Labs Limited (R&D) Plot No: DS1, IKP Knowledge park, Turkapally, Shameerpet Mandal, Hyderabad-500078, Telangana, India (IND)	Laurus Labs Limited, (VSP-2) Plot No. 19, 20 and 21, Western Sector, APSEZ, Atchutapuram, Visakhapatnam- 531011, Andhra Pradesh, India (IND)

The complete method validation report for Assay as well as its method transfer report is already part of the original submission.

Reviewer's Conclusion:

The firm provided the information of the originating laboratory and the receiving laboratory of the DP assay method. The method validation report and transfer report are provided in AM dated 02/06/2020 and original submission, respectively. The firm's response is satisfactory.

Deficiency 6: Please update module 3 to include the packaging information for commercial batches.

Summary of Firm's Response:

Satisfactory

We would like to clarify to the Agency that the packaging information for commercial batches is already part of the original dossier. Please refer Section 3.2.P.7.3 (Page 288 to 289 of 303).

Reviewer's Conclusion:

The information was provided in the original submission. The firm's response is satisfactory.

Deficiency 7: Please provide the leak test result for the blister package.

Summary of Firm's Response:

Satisfactory

The leak test for the blister packs was performed in exhibit batches and the same information was already mentioned in all the respective batch packaging record of the blister packs. The leak test result for the blister package for all Exhibit batches are tabulated below for agency's ready reference:

Strength	Blister Pack	Batch No.:	Acceptance criteria	Observation
24 mg/26 mg	Cold form	E1801034	All blister should pass leak test	Pass
		E1801134	All blister should pass leak test	Pass
		E1801214	All blister should pass leak test	Pass
	PVC/Aclar	E1801035	All blister should pass leak test	Pass
		E1801135	All blister should pass leak test	Pass
		E1801215	All blister should pass leak test	Pass
49 mg/51 mg	Cold form	E1801014	All blister should pass leak test	Pass
		E1801114	All blister should pass leak test	Pass
		E1801224	All blister should pass leak test	Pass
	PVC/Aclar	E1801015	All blister should pass leak test	Pass
		E1801115	All blister should pass leak test	Pass
		E1801225	All blister should pass leak test	Pass
97 mg/103 mg	Cold form	E1801024	All blister should pass leak test	Pass
		E1801124	All blister should pass leak test	Pass
		E1801234	All blister should pass leak test	Pass
	PVC/Aclar	E1801025	All blister should pass leak test	Pass
		E1801125	All blister should pass leak test	Pass
		E1801235	All blister should pass leak test	Pass

Reviewer's Conclusion:

The firm provided leak test for the blister package for all Exhibit batches. All passed the leak test. The blister pack size for commercial batches is different from the exhibit batches, while the materials of construction for both the packs are same. The firm's response is satisfactory.

Deficiency 8: We acknowledge that you have revised the label to include preparation of oral suspension to be in line with the RLD label in amendment dated November 07, 2019. However, your response is not supported by any developmental data demonstrating quality of the suspension. Please provide the CMC study result to support it. The study should demonstrate suspension stability stored in your proposed container/closure on microbiological attributes, dose accuracy as well as physical and chemical properties including appearance, re-suspendability, pH, particle size distribution, dissolution, assay and degradation.

Summary of Firm's Response:

Satisfactory

We acknowledge the agency's comment.

The suspension stability study on drug product was performed on the sample stored at controlled room temperature in proposed container/closure. The microbiological attributes, dose accuracy as well as physical and chemical properties including appearance, re-suspendability, pH, particle size distribution, dissolution, assay and degradation were evaluated and report is provided in Section 3.2.P.2 of this submission.

Based on the above studies, the oral suspension of the test product is stable up to 15 days in-line with the RLD label.

Reviewer's Conclusion:

The suspension stability study on drug product was performed on the sample stored at controlled room temperature in proposed container/closure i.e. amber colored PET or glass bottle. The test parameters include appearance, pH, dose accuracy, dissolution, assay, related substances, microbial limit test, PSD, and re-suspendability. All results are comparable and are within the DP specification with the exception of microbial limit test and related substances at initial and at 15th-day, as summarized in the table below. The content of related substances and microbial limit test showed upward trend but still within the current DP specifications. Should be noted that the total impurity is 0.54 on the 15th day in amber glass bottle.

	Amber Color PET Bottle		Amber Color Glass Bottle	
	0 th Day	15 th day	0 th Day	15 th day
Related substances				
Des-ethyl Impurity	BDRL	0.2	BDRL	0.2
Succinamide Impurity	BDRL	0.18	BDRL	0.19
Any unspecified impurity	BDRL	0.09	BDRL	0.06
Total impurities	BDRL	0.45	BDRL	0.54
Microbial enumeration tests and test for specified microorganisms				
Total Aerobic Microbial Count	<10 CFU/ml	20 CFU/ml	<10 CFU/ml	40 CFU/ml
Total Yeast and Mould Count	<10 CFU/ml	10 CFU/ml	<10 CFU/ml	10 CFU/ml

The suspension stability study results demonstrated that the oral suspension of the test product is stable up to 15 days, which support the labeling statement. The firm's response is satisfactory.

Deficiency 9: Please revise the post-approval stability commitment protocol to place the first three production batches of any batch size different than exhibit batch size on long term stability studies through the proposed shelf life and on accelerated studies for 6 months as per ICH Q1A (R2).

Summary of Firm's Response:

Satisfactory

We acknowledge the agency's comment.

The post-approval stability commitment protocol has been revised to place the first three production batches of any batch size different than exhibit batch size on long term stability studies through the proposed shelf life and on accelerated studies for 6 months. The revised post-approval stability commitment is provided in Section 3.2.P.8.2 of this submission.

Reviewer's Conclusion:

The firm revised the post-approval stability commitment as per the agency's request. The firm's response is satisfactory.

The relevant information in P.8 of this review has been updated.

Deficiency 10: Please be aware that we are using ICH Q1E to establish the expiration date of your drug product. Based on ICH Q1E, the stability data submitted thus far does not support your proposed 24 months expiry date. Per ICH Q1E, we encourage you to submit additional stability data to support your proposed 24 months expiration date.

Summary of Firm's Response:

Satisfactory

We acknowledge the Agency's comments.

The most updated stability data up to 12 months in-line with previous specification is provided in Section 3.2.P.8.3 of this submission. The revised specification will be implemented from the next stability time points i.e. 18 months and onwards.

Reviewer's Conclusion:

The firm provided up to 12 months long term stability data as per the original DP specification. The firm stated that the revised specification will be implemented from the 18th-month time point. The firm's response is satisfactory and the 24 months expiration date is acceptable.

Deficiency 11: Please provide all accrued room temperature stability data in your next amendment.

Summary of Firm's Response:

Not Satisfactory

Please refer to the response of Q #10.

Reviewer's Conclusion:

The firm provided up to 12 months long term stability data. All tests are within the revised DP specification with the exception of the dissolution test. No obvious trend is observed. The dissolution results meet the original dissolution specification, while some do not meet the revised dissolution specification at NLT 80% in 30 minutes at S1 stage, as summarized in the table below. The firm revised the dissolution specification from NLT 75% (Q) of Sacubitril and Valsartan in 30 minutes to NLT 80% (Q) of Sacubitril and Valsartan in 30 minutes. The biopharma review is adequate as of 2/28/2020 reviewed by Churg Chan. The reviewer checked the dissolution data under accelerated conditions which were provided in the original submission and most results meet the current specification. The product will pass the dissolution test at S2 stage. The risk on product quality is low. However, a deficiency will be conveyed to the firm regarding the dissolution.

Summary of the dissolution result that failed the revised dissolution spec. is shown in the table below.

Strength	Batch #	Time points
49 mg/51 mg	E1801224	Sacubitril OOS at 9th month at CRT
		Valsartan OOS at 9th month at CRT
	E1801115	Sacubitril OOS at 6th month at CRT
		E1801016
97 mg/103 mg	E1801226	Valsartan OOS at 6th month at CRT
	E1801021	Valsartan OOS at 12th month at CRT
		E1801121
	E1801231	
		Valsartan OOS at 6th month at CRT
		Sacubitril OOS at 6th month at ACC
	E1801232	Sacubitril OOS at 9th month at CRT
		Valsartan OOS at 9th month at CRT
	E1801024	Valsartan OOS at 6th month at CRT
	E1801124	Sacubitril OOS at 6th month at CRT
		Valsartan OOS at 6th month at CRT
	E1801234	Sacubitril OOS at 6th, 12th-month at CRT
		Valsartan OOS at 6th, 12th-month at CRT
	E1801025	Sacubitril OOS at 6th, 9th, 12th-month at CRT
		Valsartan OOS at 6th, 9th, 12th-month at CRT
	E1801125	Sacubitril OOS at 6th month at CRT
Valsartan OOS at 6th month at CRT		
E1801026	Sacubitril OOS at 9th month at CRT	
E1801126	Sacubitril OOS at 6th month at CRT	
	Valsartan OOS at 6th month at CRT	

New deficiency in review #1, IR#1:

Please be reminded that the dissolution specification has been revised to NLT 80% (Q) of Sacubitril and Valsartan in 30 minutes. As per the available stability data at controlled room temperature and under accelerated condition, your drug product did not meet the current dissolution specification at S1 stage at some time points. More stability data should be provided to demonstrate that your drug product meets the current dissolution specification. Note that sometimes Stage 2 testing, and occasionally Stage 3 testing may be needed.

Summary of the deficiencies in review #1, IR#1:

A. Drug substance:

1. We acknowledge you provided analytical method for NDMA and NDEA in drug substance. However, we could not locate the method validation report for the said method. Please provide the same.

B. Drug product

1. Please further tighten the assay limit for the drug product stability specification to be within 5% of the label claim.
2. The total impurity specification is much higher than the actually observed impurity results. Please further tightened the limit for total Impurities in your drug product release and stability specifications based upon the batch experience or justify them by comparison with RLD results acquired using the same method of analysis.
3. Please be reminded that the dissolution specification has been revised to NLT 80% (Q) of Sacubitril and Valsartan in 30 minutes. As per the available stability data at controlled room temperature and under accelerated condition, your drug product did not meet the current dissolution specification at S1 stage at some time points. More stability data should be provided to demonstrate that your drug product meets the current dissolution specification. Note that sometimes Stage 2 testing, and occasionally Stage 3 testing may be needed.

CHAPTER I: DRUG SUBSTANCE

[IQA ANDA Assessment Guide Reference](#)

Drug Substance Name	Sacubitril-Valsartan 3Na Complex
DMF Number (If Applicable)	033647
DMF Status	Inadequate - Major
DMF Holder	Laurus Labs Limited

Overall Assessment Recommendation for DS:

DRL

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.

Highlight Key Issues from Last Cycle and Their Resolution:

N/A - This is the review of original ANDA

Concise Description of Outstanding Issues:

Choose an item.

Select Number of Approved Comparability Protocols: 0

S.1 GENERAL INFORMATION

Nomenclature/Chemical name	:	Tri sodium [3-((1 <i>S</i> ,3 <i>R</i>)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl -1-butylcarbamoyl)propionate-(<i>S</i>)-3'-methyl-2'-(pentanoyl {2''-(tetrazol-5-ylate) biphenyl-4'-ylmethyl} amino)butyrate] (or) Tri sodium (4-[[<i>(1S,3R)</i> -1-([1,1'-biphenyl-4-ylmethyl-4-ethoxy-3-methyl-4-oxobutyl]amino)-4-oxobutanoate)(<i>N</i> -pentanoyl- <i>N</i> -{2'-(1 <i>H</i> -tetrazol-1-id-5-yl) [1,1'-biphenyl]-4-yl]methyl}- <i>L</i> -valinate)			
		<table border="1"> <thead> <tr> <th>Sacubitril</th> <th>Valsartan</th> </tr> </thead> <tbody> <tr> <td>4-[[<i>(1S,3R)</i>-1-([1,1'-Biphenyl] -4-ylmethyl)-4-ethoxy -3-methyl-4-oxobutyl]amino]-4-oxobutanoic acid</td> <td><i>N</i>-Pentanoyl-<i>N</i>-{[2'-(1<i>H</i>-tetrazol-5-yl)[1,1'-biphenyl] -4-yl]methyl}-<i>L</i>-valine</td> </tr> </tbody> </table>	Sacubitril	Valsartan	4-[[<i>(1S,3R)</i> -1-([1,1'-Biphenyl] -4-ylmethyl)-4-ethoxy -3-methyl-4-oxobutyl]amino]-4-oxobutanoic acid
Sacubitril	Valsartan				
4-[[<i>(1S,3R)</i> -1-([1,1'-Biphenyl] -4-ylmethyl)-4-ethoxy -3-methyl-4-oxobutyl]amino]-4-oxobutanoic acid	<i>N</i> -Pentanoyl- <i>N</i> -{[2'-(1 <i>H</i> -tetrazol-5-yl)[1,1'-biphenyl] -4-yl]methyl}- <i>L</i> -valine				
International Non-proprietary Name (INN)	:	Not reported			
Compendial Name (WHO)	:	Not reported			
United States Adopted Name (USAN)	:	Sacubitril and valsartan			
Molecular Structure	:	Sacubitril-Valsartan 3Na Complex			
Molecular Formula	:	C ₄₈ H ₅₅ N ₆ O ₈ .3Na			
CAS number	:	936623-90-4			
Relative Molecular mass	:	912.95			
Pharmacological Class	:	Angiotensin II receptor and neprilysin inhibitor for the treatment of chronic heart failure (NYHA Class II-IV) and reduced ejection fraction.			

Physical form	:	White to off-white solid
(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.

Assessment:

Adequate

(b) (4)

Assessment:
N/A

Choose an item.

R REGIONAL INFORMATION

Comparability Protocols N/A (See Below)

Assessment:

Choose an item.

Lifecycle Management Considerations

DRUG SUBSTANCE LIST OF DEFICIENCIES:

- 1.
- 2.
- 3.
- 4.

(b) (4)

CHAPTER II: DRUG PRODUCT

[IQA ANDA Assessment Guide Reference](#)

Overall Assessment Recommendation: Discipline Review Letter (DRL)

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:

Drug Product CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Review Cycle #2	Comments*
Physical stability (solid state)	36 Medium	(b)(4)	Low	(b)(4)
Chemical Stability	48 Medium		Low	
Assay	18 Low		Low	
Content uniformity	24 Low			

		(b)(4)		(b)(4)
Microbial limits	9 Low		Low	
Dissolution	48 Medium			

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 the 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. Biopharm review is inadequate.*
- *Elemental impurity compliance with ICH Q3D – status: Adequate*
- *Number of Comparability protocols included: 0*

RLD versus Generic Product – NOT FOR FOIA

(b) (4)

* For repacking purpose only

P.1 DESCRIPTION AND COMPOSITION

Component/Composition of Sacubitril and Valsartan Tablets 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg

Ingredients	Compendial Reference	Pharmaceutical Function	24mg/ 26mg	49mg/ 51mg	97mg/ 103mg	%w/w
			(mg/ Tablet)			
Intra-granular materials						
Sacubitril-Valsartan 3Na Complex [^]	In-House	Active Ingredient	(b)(4)			
Low-substituted hydroxypropylcellulose (b)(4)	USP-NF	(b)(4)				
Microcrystalline Cellulose (b)(4)	USP-NF					
Crospovidone (b)(4)	USP-NF					
Silicon dioxide (b)(4)	USP-NF					
Magnesium Stearate (b)(4)	USP-NF					
(b)(4)						
Weight of Coated Tablet			103.000	206.000	412.000	100.000

(b)(4)

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(b) (4)

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• (b)(4)

Assessment:	Inadequate
(b)(4)	

R REGIONAL INFORMATION

Environmental

- Laurus Labs Limited states that for this Abbreviated New Drug Application (ANDA) we are subject to a categorical exclusion from the requirement to prepare an Environmental Assessment Statement, as per 21 CFR § 25.30, 25.31, 25.33 and 25.15 (d).
- This ANDA is for the drug product which will not be indicated for administration at a higher dose level, nor for a longer duration, or for different indications than those that are in effect. No extraordinary circumstances, as outlined in 21 CFR § 25.21, exist. Hence, a categorical exclusion from the requirement to prepare an Environmental Assessment is hereby requested.
- Also, Laurus Labs Limited, hereby states that we are in compliance with all federal, state and local environmental laws.

Assessment: Adequate	Adequate

Methods Validation or Verification Package

Assessment:	Adequate

Comparability Protocols

Assessment: N/A	Choose an item.

Lifecycle Management Considerations

DRUG PRODUCT LIST OF DEFICIENCIES

1.

2.

3.

4.

(b) (4)

(b) (4)

5.

6.

7.

(b) (4)

8.

9.

10.

11.

(b) (4)

CHAPTER III: ENVIRONMENTAL

[IQA ANDA Assessment Guide Reference](#)

R REGIONAL INFORMATION

Environmental

- Laurus Labs Limited states that for this Abbreviated New Drug Application (ANDA) we are subject to a categorical exclusion from the requirement to prepare an Environmental Assessment Statement, as per 21 CFR § 25.30, 25.31, 25.33 and 25.15 (d).
- This ANDA is for the drug product which will not be indicated for administration at a higher dose level, nor for a longer duration, or for different indications than those that are in effect. No extraordinary circumstances, as outlined in 21 CFR § 25.21, exist. Hence, a categorical exclusion from the requirement to prepare an Environmental Assessment is hereby requested.
- Also, Laurus Labs Limited, hereby states that we are in compliance with all federal, state and local environmental laws.

Assessment:
Adequate

Adequate

CHAPTER IV: LABELING

[IQA ANDA Assessment Guide Reference](#)

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	Dimension (mm) (Length x Width)	Imprint Code
24mg/26mg	9.11x 5.08	Violet white color, oval, biconvex film-coated tablets debossed with "S5" on one side and plain on the other side.
49mg/51mg	12.75 x 5.90	Pale yellow color, oval, biconvex film-coated tablets debossed with "S1" on one side and plain on the other side.
97mg/103mg	12.57 x 6.85	Light pink color, oval, biconvex film-coated tablets debossed with "S2" on one side and plain on the other side.

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

A. Drug Substance Deficiencies

1.

(b) (4)
2.

(b) (4)

B. Drug Product Deficiencies

1.

(b)(4)

C. Labeling Deficiencies

None

(END OF DRUG PRODUCT QUALITY ASSESSMENT)

Signature Block:

Primary DP Assessor: Xihong Wang

Date: 12/19/19;
3/31/2020;
1/22/2021

Secondary DP Assessor: Marco Bennett

Date: 12/19/2019;
04.01.2020;
04.14.2020;
01.22.2021



Marco A.
Bennett

Digitally signed by Marco A. Bennett

Date: 2/11/2021 12:28:57PM

GUID: 508da705000289bae41af5c5413d8455



Xihong
Wang

Digitally signed by Xihong Wang

Date: 2/11/2021 12:21:47PM

GUID: 508da7410002ba99af7b0597dc38d164

MANUFACTURING INTEGRATED ASSESSMENT

Application ID	ANDA 213676
Drug Product Name	Sacubitril and Valsartan Tablets
Strengths	24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg
Dosage Form	Tablets
Administration Route	Oral
Indication	(b)(4)
Applicant Name	Laurus Labs Limited
RLD Number	207620

I. Manufacturing Summary

Facility Assessment Recommendation: Adequate

Process Assessment Recommendation: Adequate

Assessment Summary:

Sacubitril and Valsartan Tablets 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg is manufactured using (b)(4)

(b)(4)

The DS manufacturer, DP manufacturer, Critical Intermediate manufacturer and external testing facility are recommended for approval based on compliance history, acceptable profile codes and experience in the proposed responsibilities.

List Submissions being assessed (Table):

Document Description (SD #)	Date Received
Original (SD# 0001)	07/08/2019
Response to IR (SD# 0003)	09/16/2019
Response to IR (SD#0007)	02/06/2020
Response to IR (SD#0008)	03/02/2020
Response to CR (SD#0009)	07/01/2020

Highlight Key Issues from Last Cycle and Their Resolution: 1st Cycle

Review #1

(b)(4)

(b)(4)

Review #2

(b)(4)

Concise Description of Outstanding Issues (List bullet points with key information and update as needed):

- None

List Number of Comparability Protocols: None

1. Lifecycle Management Considerations

Post-approval inspection?	No
Lifecycle considerations	No
Choose an item.	

2. Facilities Table

Facility name and address	FEI	Responsibilities and profile code(s)	Status
Laurus Labs Limited, (b)(4) (b)(4) Plot No. 19, 20 and 21, Western Sector, APSEZ, Atchutapuram, Visakhapatnam, Andhra Pradesh, India, 531011	3011538548	(b)(4)	Approve - Based on Previous History
Laurus Labs Limited (b)(4) (b)(4) Plot No. 21, Jawaharlal Nehru Pharma City Parawada, Visakhapatnam, Andhra Pradesh, India, 531021	3007083664		Approve - Based on PAI
Laurus Labs Limited (b)(4) Plot No. 18, Jawaharlal Nehru Pharma City Parawada, Visakhapatnam, Andhra Pradesh, India, 531021	3007083664		Approve - Based on Previous History
(b)(4)			Approve - Based on PAI

(b) (4)	(In lieu of PAI, documents assessed using 704(a)(4))
	Withdrawn Per amendment dated 07/01/2020
	Approve - Based on PAI (In lieu of PAI, documents assessed using 704(a)(4))

(b) (4)

[MF033647 \(033647 - 0002 - \(2\) - 2019-07-22 - ORIG-1 /Quality/Response To Information Request\) - control-of-materials \(#4\)](#)

* Note Linhai Tianyu Pharmaceutical Co is already included in from 356h of the application.

II. Drug Product Manufacturing

1. Batch Formula

Comparative Quantitative Batch Formula Composition (Exhibit Batch vs Intended Commercial Batch)

The comparative batch formula of exhibit batches and intended commercial batches of Sacubitril and Valsartan Tablets 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg is presented in below table:

Ingredients	Quality Standard	Exhibit Batch Size (b)(4)		Intended Commercial Batch Size (b)(4)	
		Quantity per batch (kg)	Quantity per batch %(w/w)	Quantity per batch (kg)	Quantity per batch %(w/w)
Intra-granular Part					
Sacubitril-Valsartan 3Na Complex ⁵	In-House	(b)(4)			
Low-substituted hydroxypropylcellulose (b)(4)	USP-NF				
Microcrystalline Cellulose (b)(4)	USP-NF				
Crospovidone (b)(4)	USP-NF				
Silicon dioxide (b)(4)	USP-NF				
Magnesium Stearate (b)(4)	USP-NF				
(b)(4)					
(b)(4)		(b)(4)	100.00	(b)(4)	100.00

(b)(4)

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(b) (4)

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(b) (4)

V. List of Outstanding Information Request/Deficiencies:

Outstanding Deficiencies Collation Table
None

VI. Signature Block

Round#	Primary Name	Secondary & Other Names	Date of Completion	Assessment Outcome	Facility OMIR
1	Mesfin Abdi 11/12/2019	Jean Tang 12/04/2019	12/5/2019	IR	Withheld
2	Mesfin Abdi 02/13/2020	Jean Tang 02/19/2020	2/19/2020	IR	Withheld
3	Mesfin Abdi 03/03/2020 04/28/2020	Jean Tang 03/13/2020 04/29/2020	4/29/2020	Adequate	Withheld



QUALITY ASSESSMENT



4	Mesfin Abdi 12/18/2020	Jean Tang 12/23/2020	12/23/2020	Adequate	Approve



Mesfin
Abdi

Digitally signed by Mesfin Abdi
Date: 12/28/2020 01:11:07PM
GUID: 576be52c0149a21475031e6689f12115



Jean
Tang

Digitally signed by Jean Tang
Date: 1/04/2021 01:31:24PM
GUID: 502d1ab500002aff2e492acb1fd0d645

RECOMMENDATION

☐ Approval
☐ Complete Response-Minor
☒ Complete Response-Major
☐ Complete Response-Major-Facilities Only

CR-Major DMF Justification:

Inadequate selection or justification of starting materials: Submission of additional information or new batch is needed. Upon receipt, the review of this information will require substantial expenditure of FDA resources.

(b)(4)
(b)(4) : New toxicology studies are requested (b)(4)
(b)(4) 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.

(b)(4)

Facilities 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.

ANDA 213676 Assessment #1

Drug Product Name	Sacubitril and Valsartan Tablets
Dosage Form	Capsules
Strength	24mg/26mg, 49mg/51mg and 97mg/103mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Laurus Labs Limited
US agent, if applicable	PharmaQ, Inc.

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original/Initial Submission	07/07/2019	Quality
Amendment Correspondence/Amendment Verification Statement - Quality/Response To Information Request	09/16/2019	Quality
Amendment Correspondence/Amendment Verification Statement; Quality/Response to Discipline Review Letter	02/06/2020	Quality
Quality/Response To Information Request; Amendment Correspondence/Amendment Verification Statement	03/02/2020	Quality

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Master File	Xihong Wang	Marco A. Bennett
Drug Product	Xihong Wang	Marco A. Bennett
Facility	Mesfin Abdi	Jean Tang
Biopharmaceutics	Churg Chan	Om Anand
Regulatory Business Process Manager	Kevin Ninan	
Application Technical Lead	Marco A. Bennett	
Laboratory (OTR)		
Environmental		

QUALITY ASSESMENT DATA SHEET

[IQA ANDA Assessment Guide Reference](#)

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Reviewed	Comments
33647	II	Laurus Labs Limited	Sacubitril-Valsartan 3Na Complex	Inadequate -Major	12/18/2019	Xianru Sun
Other DMF: ☐ N/A ☒ (See Below)						
(b)(4)	III	(b)(4)	(b)(4)			
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					

(b)(4)	III	(b)(4)			
	IV				

B. OTHER DOCUMENTS: IND, RLD, RS, Approved ANDA

Document	Application Number	Brand Name	Description
NDA (RLD)	NDA 207620	ENTRESTO® (sacubitril and valsartan) tablets	ENTRESTO® (sacubitril and valsartan) tablets 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg, manufactured by Novartis Pharmaceuticals Corporation. Approval date: 07/07/2015

2. CONSULTS: None

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology				
CDRH-ODE				
CDRH-OC				
Clinical				
Other				

ABBREVIATED EXECUTIVE SUMMARY (CR ONLY)

[IQA ANDA Assessment Guide Reference](#)

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Major

II. QUALITY ASSESSMENT OVERVIEW

A. Drug Substance: Inadequate-Major

1. Primary Justification:

Inadequate selection or justification of starting materials: Submission of additional information or new batch is needed. Upon receipt, the review of this information will require substantial expenditure of FDA resources.

(b)(4) New
toxicology studies are requested (b)(4) and the review of these studies requires substantial expenditure of FDA resources and will potentially affect other aspects of the application and the related conclusions.

(b)(4)

2. Secondary Justification (if necessary): None
3. Tertiary Justification (if necessary): None
4. Insert additional justification below (if necessary): None

Drug Product: Inadequate-Major

1. Primary Justification: See above DS justifications.
2. Secondary Justification (if necessary): None
3. Tertiary Justification (if necessary): None
4. Insert additional justification below (if necessary): None

OPQ Labeling: Adequate

B. Manufacturing: Adequate

1. Primary Justification: None

2. Secondary Justification (if necessary): None
3. Tertiary Justification (if necessary): None
4. Insert additional justification below (if necessary): None

Facilities: Major

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

C. Biopharmaceutics: Adequate

1. Primary Justification:
2. Secondary Justification (if necessary):
3. Tertiary Justification (if necessary):
4. Insert additional justification below (if necessary)

D. Microbiology: Adequate

1. Primary Justification:
2. Secondary Justification (if necessary):
3. Tertiary Justification (if necessary):
4. Insert additional justification below (if necessary)

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)

2)

3. Drug Product Deficiencies

1)

(b) (4)

2)

3)

4)

4. Labeling Deficiencies (Please contact OGD if you identify any Labeling deficiencies with your comments)

5. Manufacturing Deficiencies

a. Facility

1)

(b) (4)

b. Process

None

6. Biopharmaceutics Deficiencies

None

7. Microbiology Deficiencies

None

8. Other Deficiencies (Specify discipline, such as Environmental)

None

Application Technical Lead Name and Date: Marco A. Bennett, 04.30.2020



Marco A.
Bennett

Digitally signed by Marco A. Bennett

Date: 4/30/2020 10:14:15AM

GUID: 508da705000289bae41af5c5413d8455

MANUFACTURING INTEGRATED ASSESSMENT

Application ID	ANDA 213676
Drug Product Name	Sacubitril and Valsartan Tablets
Strengths	24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg
Dosage Form	Tablets
Administration Route	Oral
Indication	(b)(4)
Applicant Name	Laurus Labs Limited
RLD Number	207620

I. Manufacturing Summary

Facility Assessment Recommendation: Inadequate - Major

THEME: Inadequate Facility - cGMP Withhold

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.

Process Assessment Recommendation: Adequate

Assessment Summary:

Sacubitril and Valsartan Tablets 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg is manufactured using (b)(4)

(b)(4)

List Submissions being assessed (Table):

Document Description (SD #)	Date Received
Original (SD# 0001)	07/08/2019
Response to IR (SD# 0003)	09/16/2019
Response to IR (SD#0007)	02/06/2020
Response to IR (SD#0008)	03/02/2020

Highlight Key Issues from Last Cycle and Their Resolution: 1st Cycle

Review #1

(b)(4)

Review #2

(b)(4)

Concise Description of Outstanding Issues (List bullet points with key information and update as needed):

- None

List Number of Comparability Protocols: None

1. Lifecycle Management Considerations

Post-approval inspection?	No
Lifecycle considerations	No
Choose an item.	

2. Facilities Table

Facility name and address	FEI	Responsibilities and profile code(s)	Status
Laurus Labs Limited, (b)(4) (b)(4) Plot No. 19, 20 and 21, Western Sector, APSEZ, Atchutapuram, Visakhapatnam, Andhra Pradesh, India, 531011	3011538548	(b)(4)	Approve - Based on Previous History
Laurus Labs Limited (b)(4) (b)(4) Plot No. 21, Jawaharlal Nehru Pharma City Parawada, Visakhapatnam, Andhra Pradesh, India, 531021	3007083664		Approve - Based on PAI
Laurus Labs Limited (b)(4) Plot No. 18, Jawaharlal Nehru Pharma City Parawada, Visakhapatnam, Andhra Pradesh, India, 531021	3007083664		Approve - Based on Previous History

(b) (4)

Approve -
Based on
PAI
In lieu of
PAI,
documents
assessed
using
704(a)(4)

(b)(4)

Approve -
Based on
PAI
In lieu of
PAI,
documents
assessed
using
704(a)(4)

(b) (4)

(b) (4)

II. Drug Product Manufacturing

1. *Batch Formula*

**Comparative Quantitative Batch Formula Composition
(Exhibit Batch vs Intended Commercial Batch)**

The comparative batch formula of exhibit batches and intended commercial batches of Sacubitril and Valsartan Tablets 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg is presented in below table:

Ingredients	Quality Standard	Exhibit Batch Size (b)(4)		Intended Commercial Batch Size (b)(4)	
		Quantity per batch (kg)	Quantity per batch %(w/w)	Quantity per batch (kg)	Quantity per batch %(w/w)
Intra-granular Part					
Sacubitril-Valsartan 3Na Complex ^s	In-House	(b) (4)			
Low-substituted hydroxypropylcellulose (b)(4)	USP-NF				
Microcrystalline Cellulose (b)(4)	USP-NF				
Crospovidone (b)(4)	USP-NF				
Silicon dioxide (b)(4)	USP-NF				
Magnesium Stearate (b)(4)	USP-NF				
(b)(4)		(b)(4)	100.00	(b)(4)	100.00

(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)

V. List of Outstanding Information Request/Deficiencies:

Outstanding Deficiencies Collation Table	
1.	(b) (4)

VI. Signature Block

Round#	Primary Name	Secondary & Other Names	Date of Completion	Assessment Outcome	Facility OMIR
1	Mesfin Abdi 11/12/2019	Jean Tang 12/04/2019	12/5/2019	IR	Withheld
2	Mesfin Abdi 02/13/2020	Jean Tang 02/19/2020	2/19/2020	IR	Withheld
3	Mesfin Abdi 03/03/2020 04/28/2020	Jean Tang 03/13/2020 04/29/2020	4/29/2020	Adequate	Withheld





Mesfin
Abdi

Digitally signed by Mesfin Abdi
Date: 4/30/2020 10:11:02AM
GUID: 576be52c0149a21475031e6689f12115



Jean
Tang

Digitally signed by Jean Tang
Date: 4/29/2020 02:51:50PM
GUID: 502d1ab500002aff2e492acb1fd0d645



DRUG PRODUCT QUALITY ASSESSMENT

ANDA 213676 (Review Cycle # 01, IR#1)

Sacubitril and Valsartan Tablets,

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

Xihong Wang

Division of Immediate Release Products I/Branch II

Office of Lifecycle Drug Products

Office of Pharmaceutical Quality

CR-Major DMF Justification:

Inadequate selection or justification of starting materials: Submission of additional information or new batch is needed. Upon receipt, the review of this information will require substantial expenditure of FDA resources.

(b)(4)

(b)(4) New toxicology studies are requested (b)(4) 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.

(b)(4)

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ANDA 213676 (Assessment Cycle # 01)

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	Laurus Labs Limited Second Floor, Serene Chambers, Road No.7, Banjara Hills Hyderabad, Telangana India, 500034
Drug Product Manufacturer	(b) (4)
US agent, if applicable	☐ N/A ☒ (See Below) Dr. Jose D. Gomes, Ph.D., President, PharmaQ, Inc. Waterview Plaza, 2001 Route 46, Suite 105 Parsippany, NJ 07054 Tel: +(1)-973-402-5300 Fax: +(1)-973-368-1145 Email: jgomes@pharmaq.net
Proposed Indication	(b)(4)

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original (Subject of review #1)	07/08/2019	All
Amendment: Response to DRL-Labeling dated 10/25/19 (Subject of review #1)	11/07/2019	Labeling
Amendment: Response to DRL-Labeling dated 01/03/20 (Subject of review #1, IR#1)	02/06/2020	DP, Biopharm, Process

QUALITY ASSESSMENT DATA SHEET

[IQA ANDA Assessment Guide Reference](#)

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Reviewed	Comments
33647	II	Laurus Labs Limited	Sacubitril-Valsartan 3Na Complex	Inadequate-Major	12/18/2019	Xianru Sun
Other DMF: ☐ N/A ☒ (See Below)						
(b)(4)	III	(b)(4)	(b)(4)			
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					
	III					

(b)(4)	IV	Colorcon	(b)(4)			

B. OTHER DOCUMENTS: IND, RLD, RS, Approved ANDA

Document	Application Number	Brand Name	Description
NDA (RLD)	NDA 207620	ENTRESTO® (sacubitril and valsartan) tablets	ENTRESTO® (sacubitril and valsartan) tablets 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg, manufactured by Novartis Pharmaceuticals Corporation. Approval date: 07/07/2015

2. CONSULTS: None

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology				
CDRH-ODE				
CDRH-OC				
Clinical				
Other				

PART I. Review of Firm's Response to Deficiencies

CHAPTER I: DRUG SUBSTANCE

[IQA ANDA Assessment Guide Reference](#)

Drug Substance Name	Sacubitril-Valsartan 3Na Complex
DMF Number (If Applicable)	033647
DMF Status	Inadequate - Major
DMF Holder	Laurus Labs Limited

Overall Assessment Recommendation for DS:

DRL

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.

Highlight Key Issues from Last Cycle and Their Resolution:

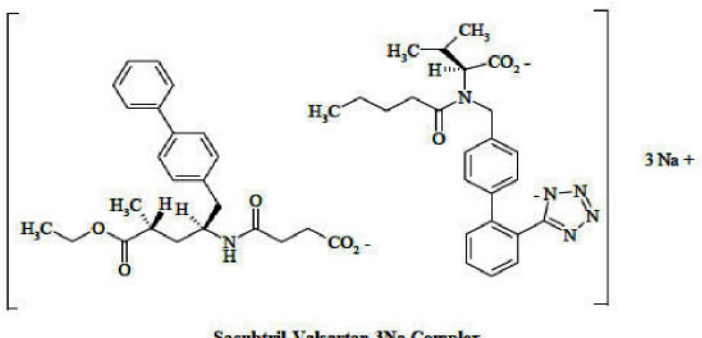
N/A - This is the review of original ANDA

Concise Description of Outstanding Issues:

Choose an item.

Select Number of Approved Comparability Protocols: 0

S.1 GENERAL INFORMATION

Nomenclature/Chemical name	: Tri sodium [3-((1 <i>S</i> ,3 <i>R</i>)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl -1-butylcarbamoyl)propionate-(<i>S</i>)-3'-methyl-2'-(pentanoyl {2''-(tetrazol-5-ylate) biphenyl-4'-ylmethyl} amino)butyrate]				
	(or) Tri sodium (4-[[[(1 <i>S</i> ,3 <i>R</i>)-1-([1,1'-biphenyl-4-ylmethyl-4-ethoxy-3-methyl-4-oxobutyl]amino)-4-oxobutanoate)(N-pentanoyl-N-{2'-(1 <i>H</i> -tetrazol-1-id-5-yl) [1,1'-biphenyl]-4-yl]methyl}-L-valinate)				
	<table border="1"> <thead> <tr> <th>Sacubitril</th> <th>Valsartan</th> </tr> </thead> <tbody> <tr> <td>4-[[[(1<i>S</i>,3<i>R</i>)-1-([1,1'-Biphenyl] -4-ylmethyl)-4-ethoxy -3-methyl-4-oxobutyl]amino]-4-oxobutanoic acid</td> <td>N-Pentanoyl-N-{[2'-(1<i>H</i>-tetrazol-5-yl)[1,1'-biphenyl] -4-yl]methyl}-L-valine</td> </tr> </tbody> </table>	Sacubitril	Valsartan	4-[[[(1 <i>S</i> ,3 <i>R</i>)-1-([1,1'-Biphenyl] -4-ylmethyl)-4-ethoxy -3-methyl-4-oxobutyl]amino]-4-oxobutanoic acid	N-Pentanoyl-N-{[2'-(1 <i>H</i> -tetrazol-5-yl)[1,1'-biphenyl] -4-yl]methyl}-L-valine
Sacubitril	Valsartan				
4-[[[(1 <i>S</i> ,3 <i>R</i>)-1-([1,1'-Biphenyl] -4-ylmethyl)-4-ethoxy -3-methyl-4-oxobutyl]amino]-4-oxobutanoic acid	N-Pentanoyl-N-{[2'-(1 <i>H</i> -tetrazol-5-yl)[1,1'-biphenyl] -4-yl]methyl}-L-valine				
International Non-proprietary Name (INN)	: Not reported				
Compendial Name (WHO)	: Not reported				
United States Adopted Name (USAN)	: Sacubitril and valsartan				
Molecular Structure	:  Sacubitril-Valsartan 3Na Complex				
Molecular Formula	: C ₄₈ H ₅₅ N ₆ O ₈ .3Na				
CAS number	: 936623-90-4				
Relative Molecular mass	: 912.95				
Pharmacological Class	: Angiotensin II receptor and neprilysin inhibitor for the treatment of chronic heart failure (NYHA Class II-IV) and reduced ejection fraction.				

Physical form	: White to off-white solid

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CHAPTER II: DRUG PRODUCT

[IQA ANDA Assessment Guide Reference](#)

Overall Assessment Recommendation: Discipline Review Letter (DRL)

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:

Drug Product CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Review Cycle #1, IR#1	Comments*
Physical stability (solid state)	36 Medium	(b)(4)	Low	(b)(4)
Chemical Stability	48 Medium		Medium	
Assay	18 Low		Low	
Content uniformity	24 Low			

		(b)(4)		(b)(4)
Microbial limits	9 Low		Low	
Dissolution	48 Medium			

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 the 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. Biopharm review is inadequate.*
- *Elemental impurity compliance with ICH Q3D – status: Adequate*
- *Number of Comparability protocols included: 0*

RLD versus Generic Product – NOT FOR FOIA

(b) (4)

* For repacking purpose only

P.1 DESCRIPTION AND COMPOSITION

Component/Composition of Sacubitril and Valsartan Tablets 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg

Ingredients	Compendial Reference	Pharmaceutical Function	24mg/ 26mg	49mg/ 51mg	97mg/ 103mg	%w/w
			(mg/ Tablet)			
Intra-granular materials						
Sacubitril-Valsartan 3Na Complex [^]	In-House	Active Ingredient	(b)(4)			
Low-substituted hydroxypropylcellulose (b)(4)	USP-NF	(b)(4)				
Microcrystalline Cellulose (b)(4)	USP-NF					
Crospovidone (b)(4)	USP-NF					
Silicon dioxide (b)(4)	USP-NF					
Magnesium Stearate (b)(4)	USP-NF					
(b)(4)						
Weight of Coated Tablet			103.000	206.000	412.000	100.000

(b)(4)

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R REGIONAL INFORMATION

Environmental

- Laurus Labs Limited states that for this Abbreviated New Drug Application (ANDA) we are subject to a categorical exclusion from the requirement to prepare an Environmental Assessment Statement, as per 21 CFR § 25.30, 25.31, 25.33 and 25.15 (d).
- This ANDA is for the drug product which will not be indicated for administration at a higher dose level, nor for a longer duration, or for different indications than those that are in effect. No extraordinary circumstances, as outlined in 21 CFR § 25.21, exist. Hence, a categorical exclusion from the requirement to prepare an Environmental Assessment is hereby requested.
- Also, Laurus Labs Limited, hereby states that we are in compliance with all federal, state and local environmental laws.

Assessment:
Adequate

Adequate

Methods Validation or Verification Package

Assessment:

Adequate

Comparability Protocols

Assessment:
N/A

Choose an item.

Lifecycle Management Considerations

DRUG PRODUCT LIST OF DEFICIENCIES

1.

2.

3.

(b) (4)

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CHAPTER III: ENVIRONMENTAL

[IQA ANDA Assessment Guide Reference](#)

R REGIONAL INFORMATION

Environmental

- Laurus Labs Limited states that for this Abbreviated New Drug Application (ANDA) we are subject to a categorical exclusion from the requirement to prepare an Environmental Assessment Statement, as per 21 CFR § 25.30, 25.31, 25.33 and 25.15 (d).
- This ANDA is for the drug product which will not be indicated for administration at a higher dose level, nor for a longer duration, or for different indications than those that are in effect. No extraordinary circumstances, as outlined in 21 CFR § 25.21, exist. Hence, a categorical exclusion from the requirement to prepare an Environmental Assessment is hereby requested.
- Also, Laurus Labs Limited, hereby states that we are in compliance with all federal, state and local environmental laws.

Assessment:
Adequate

Adequate

CHAPTER IV: LABELING

[IQA ANDA Assessment Guide Reference](#)

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	Dimension (mm) (Length x Width)	Imprint Code
24mg/26mg	9.11x 5.08	Violet white color, oval, biconvex film-coated tablets debossed with "S5" on one side and plain on the other side.
49mg/51mg	12.75 x 5.90	Pale yellow color, oval, biconvex film-coated tablets debossed with "S1" on one side and plain on the other side.
97mg/103mg	12.57 x 6.85	Light pink color, oval, biconvex film-coated tablets debossed with "S2" on one side and plain on the other side.

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

A. Drug Substance Deficiencies

1. (b) (4)
- 2.

B. Drug Product Deficiencies

- 1.
- 2.
3. (b) (4)
- 4.

C. Labeling Deficiencies

None

(END OF DRUG PRODUCT QUALITY ASSESSMENT)

Signature Block:

Primary DP Assessor: Xihong Wang

Date: 12/19/19;
3/31/3030

Secondary DP Assessor: Marco Bennett

Date: 12/19/2019;
04.01.2020;
04.14.2020



Marco A.
Bennett

Digitally signed by Marco A. Bennett

Date: 4/17/2020 08:08:25AM

GUID: 508da705000289bae41af5c5413d8455



Xihong
Wang

Digitally signed by Xihong Wang

Date: 4/16/2020 09:57:36AM

GUID: 508da7410002ba99af7b0597dc38d164

List of Deficiencies for DRL

A. Drug Substance Deficiencies

1.

(b) (4)

2.

3.

4.

B. Drug Product Deficiencies

1.

(b) (4)

2.

3.

4.

(b) (4)

5.

6.

7.

8.

(b) (4)

9.

10.

11.

C. Environmental Analysis Deficiencies**D. Labeling Deficiencies****E. Process Deficiencies**

1.

2.

3.

4.

5.

(b) (4)

6.

7.

(b) (4)

F. Facilities Deficiencies:

None

G. Biopharmaceutics Deficiencies

1. Based on the provided information and data, the proposed dissolution method (USP II at 50 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 (b)(4) dissolution acceptance criteria and therefore the proposed acceptance criterion is not acceptable. Implement the following acceptance criteria for your proposed product, Sacubitril and Valsartan Tablets:

(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.

2.

(b) (4)

[(N=12, individual, mean, CV%)] for the bio-batch and at least one batch of other strengths using this new dissolution method. (b)(4)

(b) (4)

H. Microbiology Deficiencies

None

OVERALL ASSESSMENT AND SIGNATURES:

Application Technical Lead Name and Date: Marco Bennett, 12/31/2019

MEMORANDUM

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 [redacted]
ANDA (b)(4)
ANDA
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 February 2018, which falls within the surveillance interval. The inspection was conducted under the following submissions: ANDAs [redacted] (b)(4) [redacted] (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	QPS Bioserve India Pvt., Ltd.	Plot No. 47, 2 nd Floor, Balanagar IDA, Balanagar Cross Roads, Medchal District, Hyderabad, Telangana, India

Nicola Fenty-stewart-S
Digitally signed by Nicola Fenty-stewart-S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001347020, cn=Nicola Fenty-stewart-S
Date: 2019.08.19 09:46:20 -0400

Timely Consults and Early IR Checklist for Type II API DMFs

Result: TCIR-Hidden Facility/Intermediate Facility Evaluated

ANDA#: 213676

Drug Product: SACUBITRIL AND VALSARTAN, tablet, 49mg || 51mg || 97mg || 103mg
|| 24mg || 26mg

DMF#: 033647

DMF Subject (API name): SACUBITRIL VALSARTAN 3NA COMPLEX

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). The Sacubitril synthesis from an advanced intermediate (2R,4S)-5-([1,1'-biphenyl]-4-yl)-4-((tert-butoxycarbonyl)amino)-2-Methylpentanoic acid (Boc-acid, KSM) is performed in this DMF. Valsartan only undergoes a salt conversion in this DMF. Valsartan is received as an isolated material so sameness should not be an issue for this API (two suppliers, LoAs and facility information provided). Sacubitril sodium is an isolated material that could be tested to establish identity prior to forming the mixture so there is not a sameness issue here. No LoA is provided for the sacubitril intermediate. The firm references the following DMFs for Valsartan:

Valsartan: 023584

Sacubitril intermediate: 032175

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 [#]
(b) (4)			
* 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:

Please note that there are manufacturing facilities (critical intermediate) that are included in DMF 033647 for SACUBITRIL VALSARTAN 3NA COMPLEX that were 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.

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:

n/a

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: 7/17/2019 08:59:44AM

GUID: 508da7020002879dab02d51b50cc9c3d

Timely Consults and Early IR Checklist for Type II API DMFs

Result: TCIR-NAI

ANDA#: 213676

Drug Product: SACUBITRIL AND VALSARTAN, tablet, 49mg || 51mg || 97mg || 103mg
|| 24mg || 26mg

DMF#: 033647

DMF Subject (API name): SACUBITRIL VALSARTAN 3NA COMPLEX

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). The Sacubitril synthesis from an advanced intermediate (2R,4S)-5-([1,1'-biphenyl]-4-yl)-4-((tert-butoxycarbonyl)amino)-2-Methylpentanoic acid (Boc-acid, KSM) is performed in this DMF. Valsartan only undergoes a salt conversion in this DMF. Valsartan is received as an isolated material so sameness should not be an issue for this API (two suppliers, LoAs and facility information provided). Sacubitril sodium is an isolated material that could be tested to establish identity prior to forming the mixture so there is not a sameness issue here. No LoA is provided for the sacubitril intermediate (may be acceptable as a SM). The firm references the following DMFs for Valsartan:

Valsartan: 023584

Sacubitril intermediate: 032175

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:

n/a

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: 7/17/2019 08:39:47AM

GUID: 508da7020002879dab02d51b50cc9c3d

ANDA: 213676
Company: Dr. Reddy's Laboratories Limited
Drug: Sacubitril and Valsartan Tablets
Strength: 24mg/26mg, 49mg/51mg and 97mg/103 mg

Risk Profile Performed By: Marco Bennett, Ph.D.

Drug Product CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Review Cycle #	Comments*
Physical stability (solid state)	36 Medium	(b)(4)		
Chemical Stability	48 Medium			
Assay	18 Low			
Content uniformity	24 Low			

Drug Product CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Review Cycle #	Comments*
		(b)(4)		
Microbial limits	9 Low			
Dissolution	48 Medium			

PRODUCT PROPERTY/IMPACT OF CHANGE/CQAS	PROBABILITY OF OCCURRENCE (O)	SEVERITY OF EFFECT (S)	DETECTABILITY (D)	FMECA RPN	Comment
Physical stability (solid state)	3	3	4	36 Medium	(b)(4)
Chemical stability	4	3	4	48 Medium	
Assay	2	3	3	18 Low	
Content uniformity	2-1	2	4	8 Low	

							(b)(4)
Microbial limits	1	3	3				
Dissolution	4	3	4				

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 213676

BIOEQUIVALENCE REVIEW(s)

DIVISION OF BIOEQUIVALENCE ASSESSMENT

ANDA No.	213676	
Drug Product Name	Sacubitril and Valsartan Tablets	
Strength(s)	24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg	
Applicant Name	Laurus Labs Limited	
Applicant Address	Second Floor, Serene Chambers, Road No.7, Banjara Hills Hyderabad, Telangana, India, 500034	
US Contact Name and US Mailing Address	Sharath Koripally, Senior Director RA, QA & PV, Laurus Generics Inc. 400 Connell Drive, Suite 5200 Berkeley Heights, NJ 07922 sharath.koripally@laurusgenerics.com	
US Contact Telephone Number	718-510-6822	
US Contact Fax Number	N/A	
Original Submission and Amendment(s) Date(s)	07/08/2019 (New/ANDA) 01/16/2020 (Bioequivalence/Response to Discipline Review Letter) 07/01/2020 (Resubmission/After Action- Complete; Bioequivalence/Other)	
Submission Date(s) of Amendment(s) Under Assessment	N/A*	
Primary Assessor	Alaa H. Abuznait, Ph.D.	
Secondary Assessor	Amanda Jones, Ph.D.	
Tertiary Assessor	N/A	
Study Number(s)	662/18	663/18
Study Type(s)	Fasting (Pivotal)	Fed (Pivotal)
Strength(s)	97 mg/103 mg	97 mg/103 mg
Clinical Site	QPS Bioserve India Pvt. Limited	
Clinical Site Address	# 6-56/6/1A, Opp: IDPL Factory, Balanagar, Hyderabad-500 037, Telangana, India	
Analytical Site	(b) (4)	
Analytical Site Address	(b) (4)	
Study Number(s)	060/18	059/18
Study Type(s)	Fasting (Pilot, Failed)	Fed (Pilot, Failed)
Strength(s)	97 mg/103 mg	97 mg/103 mg

Clinical Site	QPS Bioserve India Pvt. Limited		
Clinical Site Address	Same as the pivotal BE studies		
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 ☐ N/A (Waiver/Deem Bioequivalent) ¹	<u>Post October 1, 2014 ANDAs</u> ☐ To Be Determined by OSIS ☐ Pending For Cause Inspection ☒ Complete ☐ N/A (Waiver/Deem Bioequivalent) ¹	
Waiver/Deem Bioequivalent	☒ Granted ☐ Tentatively granted ☐ Not granted ☐ N/A		
QC Dissolution	☐ Pending ☒ Adequate ² ☐ Inadequate		
Formulation	☒ Adequate ☐ Inadequate		
Will Response to CR Result in a Reformulation?	☐ Possibly ☐ No ☒ N/A		
Deficiency Classification	☐ Major ☐ Minor ☒ N/A (Assessment is Adequate)		
Major Deficiency Theme	N/A		
Justification for Major Designation	N/A		
Overall Assessment Result	☒ Adequate ☐ Inadequate		
Product Specific Guidance (PSG) Referenced in Assessment	☒ Recommended/Latest Revision Date: April 2016 ³ RLD Number: NDA 207620 ☐ N/A (no PSG available at time of assessment)		
Revised/New Draft Guidance Generated as Part of Current Assessment	☐ YES ☒ NO		
Bioequivalence study tracking/supporting document #	Study/Test Type	Strength	Assessment Result
1, 6, 9	Pivotal Fasting	97 mg/103 mg	☒ Adequate ☐ Inadequate
1, 6, 9	Pivotal Fed	97 mg/103 mg	☒ Adequate ☐ Inadequate
1	Failed Pilot Fasting	97 mg/103 mg	For Information Purposes Only

¹ Requests submitted under 21 CFR 320.22(d)(2) or 320.24(b)(6).

² GDRP: ANDA-213676-ORIG-1, Biopharmaceutics Review, A213676 Biopharm R01-AQ.pdf, 4/30/2020.
<https://panorama.fda.gov/task/view?ID=5d235adc000657983d6c5c46d380ccd0>

³ Product-Specific Guidance on Sacubitril and Valsartan Tablets (Recommended Apr 2016),
https://www.accessdata.fda.gov/drugsatfda_docs/psg/Sacubitril:%20Valsartan_oral%20tablet_RLD%207620_RC04-16.pdf accessed 8/23/2021.

1	Failed Pilot Fed	97 mg/103 mg	For Information Purposes Only
1, 6, 9	Waiver	24 mg/26 mg, 49 mg/51 mg	☒ Adequate ☐ Inadequate

N/A = Not Available.

* The current assignment was made under the 5/3/2021 submission.

1 EXECUTIVE SUMMARY

This is an addendum to the bioequivalence (BE) amendment assessment of ANDA 213676 finalized on 12/17/2020⁴ and found adequate. The impetus of 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.

The RLD labeling includes details on how to prepare suspension from 49 mg/51 mg strength of the tablet using Ora-Plus[®] and Ora-Sweet[®] SF. The RLD labeling also states that *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 2](#) for details). Furthermore, at this time, no additional data will be requested from the applicant to demonstrate BE of suspension of the test and reference products (please refer to [Section 3](#) for details). The above is consistent with the discussion on 8/10/2021 within Division of Bioequivalence I (DBI) regarding the current 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.

As discussed in the BE amendment assessment dated 12/17/2020⁴, the fasting and fed BE studies comparing the test product, Laurus Labs Limited's Sacubitril and Valsartan Tablets, 97 mg/103 mg, to the corresponding reference standard (RS) product, Novartis Pharmaceuticals Corp's ENTRESTO (sacubitril and valsartan) Tablets, 97 mg/103 mg (NDA 207620, approved on 7/7/2015⁵) remain adequate. The formulation of all strengths of the test product remains adequate from BE perspective, and the dissolution data were found adequate to support the waiver requests for the 24 mg/26 mg and 49 mg/51 mg strengths.

Therefore, the Division of Bioequivalence I (DBI)'s decision to grant the waiver request for in vivo BE study requirements for the 24 mg/26 mg and 49 mg/51 mg strengths based on criteria set forth in 21 CFR § 320.22 (d)(2) remains unchanged.

⁴ GDRP: ANDA-213676-ORIG-1-AMEND-9, Bioequivalence Review, A213676N000DB-Review01-Amend07012020.pdf, 12/17/2020.

<https://panorama.fda.gov/task/view?ID=5efdf541005a5cf12011e87420a5dded>

⁵ Electronic Orange Book,

https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=207620, accessed 8/23/2021.

The Office of Study Integrity and Surveillance (OSIS) inspection status of the current ANDA is complete for both the clinical and analytical sites.

The application remains **adequate**.

NOTE TO REGULATORY PROJECT MANAGER (RPM):

The bioequivalence assessment outcome does not change. No letter will be communicated to the applicant as a result of this addendum.

Per OGD Policy, as of 8/16/2021, there is a Policy Alert regarding the RLD ENTRESTO® (sacubitril and valsartan) Tablets stemming from Citizen Petition (CP) FDA-2019-P-1893. In addition, there is another policy alert regarding multiple drug products containing valsartan stemming from CP FDA-2019-P-2869. It is noted that the scope of this CP includes the current drug product, among other valsartan containing drug products.

No Approval Actions (AP/TA) can be taken prior to contacting Policy Lead and all disciplines can continue communications (CRL, IR/DRL). CC should contact Policy if related to CP.

2 FORMULATION DATA

2.1 Test Formulation⁶

Ingredients	Compendial Reference	Pharmaceutical Function	24 mg/ 26 mg	49 mg/ 51 mg	97 mg/ 103 mg	%w/w
			(mg/ Tablet)			
Intra-granular materials						
Sacubitril-Valsartan 3Na Complex [^]	In-House	Active Ingredient	(b)(4)			
Low-substituted hydroxypropylcellulose (b)(4)	USP-NF	(b)(4)				
Microcrystalline Cellulose (b)(4)	USP-NF					
Crospovidone (b)(4)	USP-NF					
Silicon Dioxide (b)(4)	USP-NF					
Magnesium Stearate (b)(4)	USP-NF					
(b)(4)						
Weight of Coated Tablet			103.000	206.000	412.000	100.000

(b)(4)

⁶ EDR: ANDA 213676, New/ANDA, 07/08/2019. [\CDSESUB1\evsprod\anda213676\0001\m3\32-body-data\32p-drug-prod\sacu-and-valsartan-tab-tablets\32p1-desc-comp\description-and-composition.pdf](#).

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.

2.4 Inactive Ingredients (IIG Table)-for Microcrystalline Cellulose

Inactive Ingredients Guide (IIG) Levels							
Component	Amount (mg)/ Tablet	MDI [4 Tablets] (mg)*	FDA's IIG Limit (mg, Route of Administration)	MDI (mg) from Suspension (400 mg)	Combined MDI from Tablets and Suspension (mg)	IIG Limit Reference	MDI Below or Exceeding FDA's IIG Limit
Microcrystalline Cellulose			(b)(4)				Below
MDD used for calculation			(b)(4)				
(b)(4)							
(b)(4)							

Comments on Formulation: Acceptable

- The formulation of the test product, as tablet, was previously evaluated and found acceptable⁹. The RLD labeling includes details on how to prepare suspension from 49 mg/51 mg strength of the tablet using Ora-Plus[®] and Ora-Sweet[®] SF. The RLD labeling also states that *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. However, this additional analysis is limited to the current scenario and may not necessarily apply to other products and situations.

⁸ IIG-MDD Master Spreadsheet: file://fda.gov/wodc/cder/ogd/ai/ogds11/division/bio/bio2/iig-mdd%20spreadsheet/iig-mdd_master%20spreadsheet_Final.xls, accessed 8/23/2021.

⁹ GDRP: ANDA-213676-ORIG-1, Bioequivalence Review, A213676N000DB-Review01-07082019.docx, 1/14/2020. <https://panorama.fda.gov/task/view?ID=5d235adc000654bc857251140427103a>

- The use of Ora-Plus[®] and Ora-Sweet[®] SF has been approved for preparation of suspension for RLD product. 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 suspending agents which also are present in 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.

• (b) (4)

- Per the Recommended Dose Titration table from the RLD labeling, based on the assessor's calculation, the MDD per each pediatric patient group is 6.2 mg/kg, 144/156 mg and 194/206 mg for less than 40 kg, 40 to 50 kg and greater than 50 kg, respectively (see table below). It should be noted that the dose of sacubitril and valsartan is also presented as combination of the two drug components per the RLD labeling. For example, ENTRESTO 800 mg¹¹/200 mL oral suspension is prepared in a concentration of 4 mg/mL (sacubitril/valsartan 1.96/2.04 mg/mL). To aid the calculation, the combined dose is used in first column from the right in the table below.

	Titration Step Dose (twice daily)			MDD	MDD (sacubitril + valsartan)
	Starting	Second	Final		
Pediatric patients less than 40 kg	1.6 mg/kg	2.3 mg/kg	3.1 mg/kg	(b)(4)	
Pediatric patients at least 40 kg, less than 50 kg	24/26 mg	49/51 mg	72/78 mg		
Pediatric patients at least 50 kg	49/51 mg	72/78 mg	97/103 mg		

^ This is also the MDD for adult population.

(b) (4)

- Based on 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)

- Accordingly, the assessor finds that the suspension formulation when prepared using Ora-Plus[®] and Ora-Sweet SF[®] does not pose additional issue from the IIG perspective hence is adequate.

- (b) (4)

- In summary, the suspension formulation of the test product when prepared with Ora-Plus and Ora-Sweet SF as instructed in the RLD labeling would not pose any safety concerns from the IIG perspective.
- The formulation of suspension prepared from the test product is **acceptable**.

3 ADDITIONAL CONSIDERATION RELATED TO SUSPENSION OF TEST PRODUCT

- The current Draft Guidance for Industry, Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA (August 2021¹²) 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[®] SF) may be similar to mixing the drug product with a beverage. Nonetheless, in line with the discussion on 8/10/2021 within DBI for the current 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. This

(b)(4)

(b)(4)

The bioequivalence has also been demonstrated for the tablets of the test and reference products; therefore, the risk is considered low.

NOTE TO REGULATORY PROJECT MANAGER (RPM):

The bioequivalence assessment outcome does not change. No letter will be communicated to the applicant as a result of this addendum.

Per OGD Policy, as of 8/16/2021, there is a Policy Alert regarding the RLD ENTRESTO[®] (sacubitril and valsartan) Tablets stemming from Citizen Petition (CP) FDA-2019-P-1893. In addition, there is another policy alert regarding multiple drug products containing valsartan stemming from CP FDA-2019-P-2869. It is noted that the scope of this CP includes the current drug product, among other valsartan containing drug products.

No Approval Actions (AP/TA) can be taken prior to contacting Policy Lead and all disciplines can continue communications (CRL, IR/DRL). CC should contact Policy if related to CP.

¹² <https://www.fda.gov/media/87219/download>, accessed 8/23/2021.

4 OUTCOME**Completed Assignment for 213676 ID: 46064****Assessor:** AbuZnait, Alaa**Date Completed:****Verifier:** ,**Date Verified:****Division:** Division of Bioequivalence**Description:** Sacubitril and Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg, ANDA Addendum (not for Clarification or Error Correction)*Items:*

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Score</i>	<i>Subtotal</i>
46064	7/1/2020	BIO	Addendum [1]	1	1
46064	7/1/2020	Parallel	Addendum (not for Clarification or Error Correction [1])	1	1
				Total:	2

DIVISION OF BIOEQUIVALENCE ASSESSMENT

ANDA No.	213676	
Drug Product Name	Sacubitril and Valsartan Tablets	
Strength(s)	24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg	
Applicant Name	Laurus Labs Limited	
Applicant Address	Second Floor, Serene Chambers, Road No.7, Banjara Hills Hyderabad, Telangana, India, 500034	
US Contact Name and US Mailing Address	Dr. Jose D. Gomes, Ph.D., President, PharmaQ, Inc. Waterview Plaza, 2001 Route 46, Suite 105 Parsippany, NJ 07054 jgomes@pharmaq.net	
US Contact Telephone Number	+(1)-973-402-5300	
US Contact Fax Number	+(1)-973-368-1145	
Original Submission and Amendment(s) Date(s)	07/08/2019 (New/ANDA) 01/16/2020 (Bioequivalence/Response to Discipline Review Letter) 07/01/2020 (Resubmission/After Action- Complete; Bioequivalence/Other)	
Submission Date(s) of Amendment(s) Under Assessment	N/A*	
Primary Assessor	Alaa H. Abuznait, Ph.D.	
Secondary Assessor	Amanda Jones, Ph.D.	
Tertiary Assessor	N/A	
Study Number(s)	662/18	663/18
Study Type(s)	Fasting (Pivotal)	Fed (Pivotal)
Strength(s)	97 mg/103 mg	97 mg/103 mg
Clinical Site	QPS Bioserve India Pvt. Limited	
Clinical Site Address	# 6-56/6/1A, Opp: IDPL Factory, Balanagar, Hyderabad-500 037, Telangana, India	
Analytical Site	(b)(4)	
Analytical Site Address	(b)(4)	
	060/18	059/18
	Fasting (Pilot, Failed)	Fed (Pilot, Failed)
	97 mg/103 mg	97 mg/103 mg

(b) (4)

Office of Study Integrity and Surveillance (OSIS) status	Backlog, Year 1 and Year 2 ANDAs ☐ Pending ☐ Complete ☐ N/A (Waiver/Deem Bioequivalent) ¹	Post October 1, 2014 ANDAs ☐ To Be Determined by OSIS ☐ Pending For Cause Inspection ☒ Complete ☐ N/A (Waiver/Deem Bioequivalent) ¹	
Waiver/Deem Bioequivalent	☒ Granted ☐ Tentatively granted ☐ Not granted ☐ N/A		
QC Dissolution	☐ Pending ☒ Adequate ² ☐ Inadequate ☐ N/A		
Formulation	☒ Adequate ☐ Inadequate		
Will Response to CR Result in a Reformulation?	☐ Possibly ☐ No ☒ N/A		
Deficiency Classification	☐ Major (Deficiencies to be communicated by CR) ☐ Minor/IR ☒ N/A (Assessment is Adequate)		
Major Deficiency Theme	N/A		
Justification for Major Designation	N/A		
Overall Assessment Result	☒ Adequate ☐ Inadequate		
Product Specific Guidance (PSG) Referenced in Assessment	☒ Recommended/Latest Revision Date: April 2016 ³ RLD Number: NDA 207620 ☐ N/A (no PSG available at time of assessment)		
Revised/New Draft Guidance Generated as Part of Current Assessment	☐ YES ☒ NO		
Bioequivalence study tracking/supporting document #	Study/ Test Type	Strength	Assessment Result
1, 6, 9	Pivotal Fasting	97 mg/103 mg	☒ Adequate ☐ Inadequate

¹ Requests submitted under 21 CFR 320.22(d)(2) or 320.24(b)(6).

² GDRP: ANDA-213676-ORIG-1, Biopharmaceutics Review, A213676 Biopharm R01-AQ.pdf, 4/30/2020. <https://panorama.fda.gov/task/view?ID=5d235adc000657983d6c5c46d380ccd0>

³ Product-Specific Guidance on Sacubitril and Valsartan Tablets (Recommended Apr 2016), https://www.accessdata.fda.gov/drugsatfda_docs/psg/Sacubitril:%20Valsartan_oral%20tablet_RLD%20207620_RC04-16.pdf, accessed 12/17/2020.

1, 6, 9	Pivotal Fed	97 mg/103 mg	☒ Adequate ☐ Inadequate
1	Failed Pilot Fasting	97 mg/103 mg	For Information Purposes Only
1	Failed Pilot Fed	97 mg/103 mg	For Information Purposes Only
1, 6, 9	Waiver	24 mg/26 mg, 49 mg/51 mg	☒ Adequate ☐ Inadequate

N/A = Not Available.

*The current assignment was made under the 07/01/2020 submission.

1 EXECUTIVE SUMMARY

This is an addendum to the Bioequivalence (BE) amendment assessment of ANDA 213676 finalized on 4/6/2020⁴. The impetus of this addendum is to correct an error on page 1 (cover page) of the aforementioned BE amendment assessment.

In the BE amendment assessment, the title of the cover page incorrectly includes the line “BCS Waiver” implying that the application includes a waiver request of *in vivo* BE study requirements based on Biopharmaceutics Classification System (BCS), which is incorrect as the application only includes a waiver request of *in vivo* BE study requirements for the 24 mg/26 mg and 49 mg/51 mg strengths based on criteria set forth in 21 CFR § 320.22 (d)(2).

Thus, in the current addendum, the assessor corrected the title of the cover page by omitting the line “BCS Waiver”. No additional changes to the BE amendment assessment was made.

As discussed in the BE amendment assessment dated 12/17/2020⁵, the fasting and fed BE studies comparing the test product, Laurus Labs Limited’s Sacubitril and Valsartan Tablets, 97 mg/103 mg, to the corresponding reference standard (RS) product, Novartis Pharmaceuticals Corp’s ENTRESTO® (sacubitril and valsartan) Tablets, 97 mg/103 mg (NDA 207620, approved on 7/7/2015⁶) remain adequate. The formulation of all strengths of the test product are acceptable, and the dissolution data were found adequate to support the waiver requests for the 24 mg/26 mg and 49 mg/51 mg strengths.

⁴ GDRP: ANDA-213676-ORIG-1, Bioequivalence Review, A213676N000DB-Review02-DRLResponse01162020.pdf, 4/6/2020.

<https://panorama.fda.gov/task/view?ID=5d235adc000654bc857251140427103a>

⁵ GDRP: ANDA-213676-ORIG-1-AMEND-9, Bioequivalence Review, A213676N000DB-Review01-Amend07012020.pdf, 12/17/2020.

<https://panorama.fda.gov/task/view?ID=5efdf541005a5cf12011e87420a5ddd>

⁶ Electronic Orange Book,

https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=207620, accessed 12/17/2020.

Therefore, the Division of Bioequivalence I (DBI)'s decision to grant the waiver request for in vivo BE study requirements for the 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 Office of Study Integrity and Surveillance (OSIS) inspection status of the current ANDA is complete for both the clinical and analytical sites.

The application remains **adequate**.

NOTE TO REGULATORY PROJECT MANAGER (RPM):

The bioequivalence outcome does not change. No letter will be communicated to the applicant as a result of this addendum.

Per OGD Policy, as of 12/18/2020, there is a Policy Alert regarding the RLD ENTRESTO® (sacubitril and valsartan) Tablets stemming from Citizen Petition (CP) FDA-2019-P-1893. In addition, there is another policy alert regarding multiple drug products containing valsartan stemming from CP FDA-2019-P-2869. It is noted that the scope of this CP includes the current drug product, among other valsartan containing drug products.

No Approval Actions (AP/TA) can be taken prior to contacting Policy Lead and all disciplines can continue communications (CRL, IR/DRL). CC should contact Policy if related to CP.

2 OUTCOME

Completed Assignment for 213676 ID: 44099

Assessor: AbuZnait, Alaa

Date Completed:

Verifier: ,

Date Verified:

Division: Division of Bioequivalence

Description: Sacubitril and Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg, ANDA Addendum (Error Correction)

Items:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Score</i>	<i>Subtotal</i>
44099	1/16/2020	BIO	Addendum [1]	1	1
44099	1/16/2020	Parallel	Addendum (for clarification or Error Correction [0]	0	0
				Total:	1

BIOPHARMACEUTICS ANDA REVIEW	
Application No.	ANDA-213676-ORIG-1
Applicant	Laurus Labs Limited
Product Name/ Strength(s)	Sacubitril and Valsartan Tablets/ 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg
Dosage Form/Route	Immediate-Release Tablets/Oral
Indication	Reduce the risk of cardiovascular death and hospitalization for heart failure
Submission Date(s)	7/8/2019 – Original Submission 2/6/2020 – Response to Information Request
RLD/RS	Entresto® Tablets [N207620]
Primary Reviewer	Churg Chan, Pharm.D.
Secondary Reviewer	Om Anand, Ph.D.
Recommendation	Adequate

EXECUTIVE SUMMARY:

This Biopharmaceutics Review evaluates data supporting the adequacy of the proposed dissolution method and acceptance criteria for quality control testing of the proposed drug product.

Dissolution Method:

(b)(4)

Based on the provided information and data, the proposed dissolution method (Table 1) is deemed adequate for quality control testing of the proposed product. The Applicant’s originally proposed dissolution acceptance criteria were (b)(4) and therefore not acceptable. Based on the provided data, the Applicant was recommended via an Information Request dated January 3, 2020 to revise the dissolution acceptance criteria to (b)(4)

(b)(4) and “NLT ⁽⁰⁰⁴⁾ % (Q) of Sacubitril and Valsartan in 30 minutes” for the 49 mg/51 mg and 97 mg/103 mg strengths of the proposed drug product. In a response dated February 6, 2020, the Applicant accepted the FDA recommendation regarding the dissolution acceptance criterion for the 49 mg/51 mg and 97 mg/103 mg strengths, however, they proposed “NLT ⁽⁰⁰⁴⁾ % (Q) of Sacubitril and Valsartan in 30 minutes” for the 24 mg/26 mg strength as well. Based on the totality of the information/data submitted, the newly proposed dissolution acceptance criterion and the response is acceptable.

¹ [FDA Recommended Dissolution Methods](#)

Table 1. Approved dissolution method and acceptance criteria²

Method Source	USP Apparatus	Speed	Medium	Volume/ Temperature	Recommended Acceptance Criteria
FDA – Database	II (Paddle)	50 RPM	pH 6.8 Phosphate Buffer	900 mL/ 37 ± 0.5°C	NLT $\frac{Q}{100}$ % (Q) of Sacubitril in 30 minutes NLT $\frac{Q}{100}$ % (Q) of Valsartan in 30 minutes

Recommendation:

From a Biopharmaceutics perspective, ANDA 213676 for the proposed Sacubitril/Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg, is recommended for **approval**.

² [Application 213676 - Sequence 0001 - Pharmaceutical Development Report](#)

BIOPHARMACEUTICS REVIEW

1. **Drug Substance Solubility:** (b)(4)

(b)(4)

2. **Formulation:** (b)(4)

(b)(4)

3. **Bioequivalence:** The Applicant performed *in vivo* pharmacokinetic studies using the 97 mg/103 mg strength of the proposed and RLD products in both fasting and fed conditions.⁶ Under fasting conditions, the T_{max} of Sacubitril and Valsartan were 0.71 and 2.14 hours, respectively.⁷ Under fed conditions, the T_{max} of Sacubitril and Valsartan were 1.83 hours and 3.31 hours, respectively.⁸ The Division of Bioequivalence/OGD will evaluate the bioequivalence study results and the biowaiver request.

4. **Dissolution Method:** (b)(4)

(b)(4)

The Applicant evaluated discriminating ability of the proposed dissolution method on changes of high-risk formulation variables (b)(4)

(b)(4)

(b)(4) The dissolution profiles were similar across the formulations evaluated with the proposed dissolution method. However, based on the totality of the provided data and information, the proposed dissolution method is deemed adequate for quality control testing of the proposed product.

In an Information Request dated January 3, 2020, the Applicant was asked to submit dissolution data using the new dissolution method described in the FDA's dissolution database

³ [Application 213676 - Sequence 0001 - Quality Overall Summary - Drug Substance \(PDF\)](#)

⁴ [Application 213676 - Sequence 0001 - Description of Manufacturing Process and Process Controls](#)

⁵ [Application 213676 - Sequence 0001 - Description and Composition of the Drug Product](#)

⁶ [Application 213676 - Sequence 0001 - Tabular Listing of All Clinical Studies \(Pivotal Batch\)](#)

⁷ [Application 213676 - Sequence 0001 - Clinical Study Report Body - Fasting Study](#)

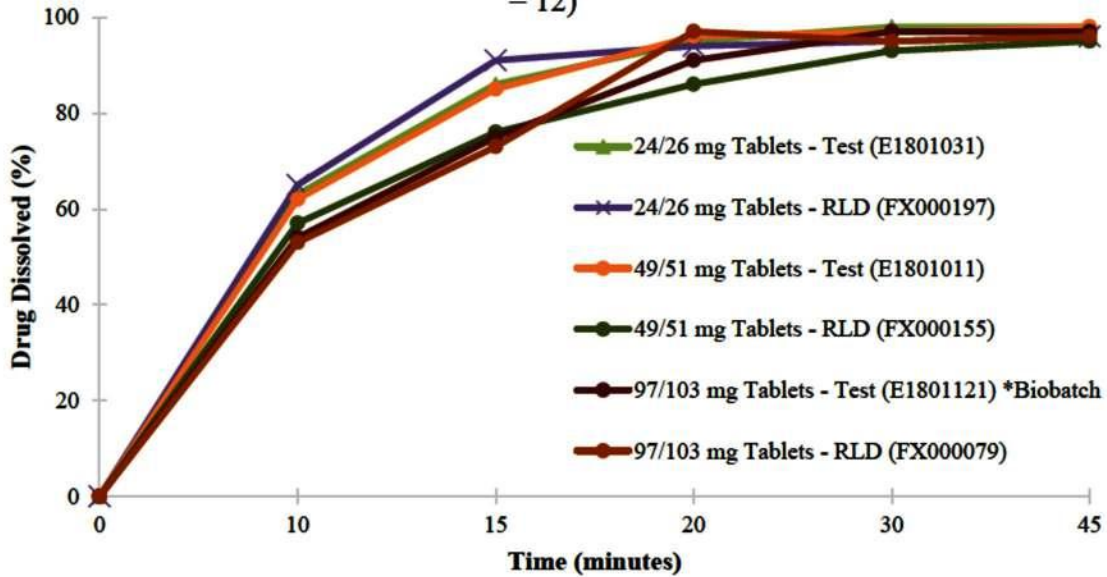
⁸ [Application 213676 - Sequence 0001 - Clinical Study Report Body - Fed Study](#)

(b)(4)

(b)(4) The dissolution data generated from this new dissolution method show dissimilarity between the biobatch and the exhibit batches ($f_2 < 50$). The Applicant proposed to continue using their original dissolution method for their proposed drug product [900 mL of pH 6.8 phosphate buffer using USP Apparatus II (Paddle) at 50 rpm].

5. Dissolution Data:¹¹

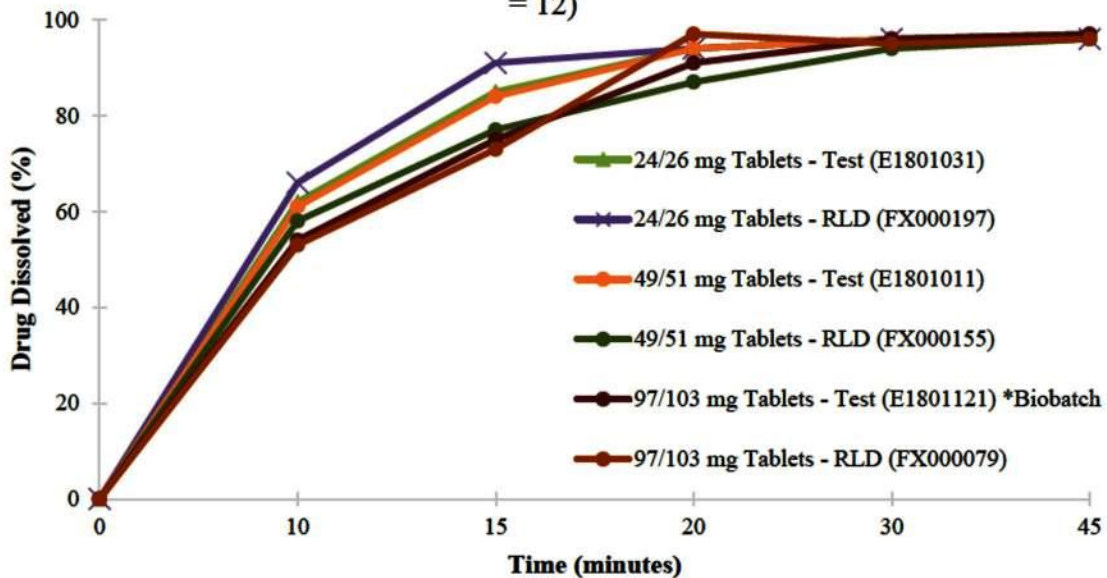
Figure 1. Summary of mean *in vitro* dissolution data for Sacubitril ($n = 12$)



¹⁰ [Application 213676 - Sequence 0007 - Comparative In-Vitro Dissolution Data](#)

¹¹ [Application 213676 - Sequence 0001 - Clinical Summary \(PDF\)](#)

Figure 2. Summary of mean *in vitro* dissolution data for Valsartan (*n* = 12)



- 6. Dissolution Acceptance Criteria:** The original dissolution acceptance criteria proposed by the Applicant, (b)(4) not supported by the data. The Applicant was recommended via an Information Request dated January 3, 2020 to implement the dissolution acceptance criteria of (b)(4) (b)(4) and “NLT 90% (Q) of Sacubitril and Valsartan at 30 minutes” for the 49 mg/51 mg and 97/103 mg strength tablets for the proposed drug product. In a response dated February 6, 2020, the Applicant accepted the FDA recommendation regarding the dissolution acceptance criterion for the 49 mg/51 mg and 97 mg/103 mg strengths, however, they proposed “NLT 90% (Q) of Sacubitril and Valsartan in 30 minutes” for the 24 mg/26 mg strength as well. The Applicant justified their proposition by reviewing data at (b)(4) 30 minutes for all their exhibit batches and the RLD. Both the proposed and reference drug product have individual unit values (b)(4) % at the (b)(4) (b)(4) time point, (b)(4). Therefore, based on the totality of the provided data and information, the Applicant’s proposed acceptance criteria are acceptable.
- 7. Stability:** The Applicant provided stability data for exhibit batches of Sacubitril and Valsartan tablets for 6 months under long-term (25° ± 2°C/60% ± 5% RH) and accelerated (40° ± 2°C/75% ± 5% RH) conditions.¹² No significant changes in dissolution in stability were observed using the proposed dissolution method.
- 8. Dissolution Risk/Mitigation Assessment:** The biopharmaceutics and dissolution risk are relatively high because (b)(4)

¹² [Application 213676 - Sequence 0001 - Stability Summary and Conclusion](#)

Applicant's BCS claims. The dissolution acceptance criteria are adequately selected to mitigate the risk of dissolution failure for the proposed drug product.

Biopharmaceutics Information Request

The following Biopharmaceutics Information Request (IR) comments were conveyed to the Applicant on January 3, 2020:

1. Based on the provided information and data, the proposed dissolution method (USP II at 50 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 (b)(4) dissolution acceptance criteria and therefore the proposed acceptance criterion is not acceptable. Implement the following acceptance criteria for your proposed product, Sacubitril and Valsartan Tablets:

(b)(4)

Sacubitril and Valsartan Tablets 49 mg/51 mg and 97/103 mg strengths
“NLT (b)(4) % (Q) of in 30 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.

2.

(b)(4)

(b)(4) Please submit dissolution data [(N=12, individual, mean, CV%)] for the bio-batch and at least one batch of other strengths using this new dissolution method. (b)(4)

(b)(4)

The Applicant responded to the above Biopharmaceutics Information Request (IR) on February 6, 2020 and accepted the recommended dissolution acceptance criteria of $Q = (b)(4)\%$ at 30 minutes for the 49 mg/51 mg and 97 mg/103 mg strengths. The Applicant also proposed the same dissolution acceptance criterion of $Q = (b)(4)\%$ at 30 minutes for their 24 mg/26 mg strength. The Applicant provided dissolution data using the new FDA dissolution database method, however, they proposed to continue using their originally proposed dissolution method. Given the available data, the response is acceptable.



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Date: 2/28/2020 10:00:25AM
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DIVISION OF BIOEQUIVALENCE ASSESSMENT

ANDA No.	213676	
Drug Product Name	Sacubitril and Valsartan Tablets	
Strength(s)	24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg	
Applicant Name	Laurus Labs Limited	
Applicant Address	Second Floor, Serene Chambers, Road No.7, Banjara Hills Hyderabad, Telangana, India, 500034	
US Contact Name and US Mailing Address	Dr. Jose D. Gomes, Ph.D., President, PharmaQ, Inc. Waterview Plaza, 2001 Route 46, Suite 105 Parsippany, NJ 07054 jgomes@pharmaq.net	
US Contact Telephone Number	973-402-5300	
US Contact Fax Number	973-368-1145	
Original Submission Date(s)	07/08/2019 (Form 3674; User Fee/Coversheet; New/ANDA)	
Submission Date(s) of Amendment(s) Under Assessment	N/A	
Primary Assessor	Alaa H. Abuznait, Ph.D.	
Secondary Assessor	Amanda Jones, Ph.D.	
Tertiary Assessor	N/A	
Study Number(s)	662/18	663/18
Study Type(s)	Fasting (Pivotal)	Fed (Pivotal)
Strength(s)	97 mg/103 mg	97 mg/103 mg
Clinical Site	QPS Bioserve India Pvt. Limited	
Clinical Site Address	# 6-56/6/1A, Opp: IDPL Factory, Balanagar, Hyderabad-500 037, Telangana, India	
Analytical Site	(b) (4)	
Analytical Site Address	(b) (4)	
Study Number(s)	060/18	059/18
Study Type(s)	Fasting (Pilot, Failed)	Fed (Pilot, Failed)
Strength(s)	97 mg/103 mg	97 mg/103 mg
Clinical Site	QPS Bioserve India Pvt. Limited	
Clinical Site Address	Same as the pivotal BE studies	
Analytical Site	(b) (4)	

Analytical Site Address	(b)(4)		
Office of Study Integrity and Surveillance (OSIS) status	<u>Backlog, Year 1 and Year 2 ANDAs</u> ☐ Pending ☐ Complete ☐ N/A (Waiver/Deem Bioequivalent) ¹		<u>Post October 1, 2014 ANDAs</u> ☒ To Be Determined by OSIS (Clinical Site) ☐ Pending For Cause Inspection ☒ Complete (Analytical Site) ☐ N/A (Waiver/Deem Bioequivalent) ¹
Waiver/Deem Bioequivalent	☐ Granted ☐ Tentatively granted ☒ Not granted ☐ N/A		
QC Dissolution	☒ Pending ☐ Adequate ☐ Inadequate		
Formulation	☒ Adequate ☐ Inadequate		
Will Response to CR Result in a Reformulation?	☐ Possibly ☒ No ☐ N/A		
Deficiency Classification	☒ Major ☐ Minor/IR ☐ N/A (Assessment is Adequate)		
Major Deficiency Theme	Bioanalytical Deficiencies		
Justification for Major Designation	The bioequivalence deficiency(ies) has/have been classified as MAJOR because the deficiencies pertain to insufficient validation data (i.e., deficiency regarding the impact of the metabolite of sacubitril on the analysis of valsartan and sacubitril in the pivotal fasting and fed BE studies) as noted in Appendix A, Section B.1.d of the Guidance for Industry, ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). The assessment of the response will require, in FDA’s judgment, a substantial expenditure of FDA resources.		
Overall Assessment Result	☐ Adequate ☒ Inadequate		
Product-Specific Guidance (PSG) Referenced in Assessment	☒ Recommended/Latest Revision Date: April 2016 ² RLD Number: NDA 207620 ☐ N/A (no PSG available at time of assessment)		
Revised/New Draft Guidance Generated as Part of Current Assessment	☐ YES ☒ NO		
Bioequivalence study tracking/supporting document #	Study/Test Type	Strength	Assessment Result
1	Pivotal Fasting	97 mg/103 mg	☐ Adequate ☒ Inadequate

¹ Requests submitted under 21 CFR 320.22(d)(2) or 320.24(b)(6).

² Product-Specific Guidance on Sacubitril and Valsartan Tablets (Recommended Apr 2016), https://www.accessdata.fda.gov/drugsatfda_docs/psg/Sacubitril:%20Valsartan_oral%20tablet_RLD%207620_RC04-16.pdf accessed 11/12/2019.

1	Pivotal Fed	97 mg/103 mg	☐ Adequate ☒ Inadequate
1	Failed Pilot Fasting	97 mg/103 mg	For Information Purposes Only
1	Failed Pilot Fed	97 mg/103 mg	For Information Purposes Only
1	Waiver	24 mg/26 mg, 49 mg/51 mg	☐ Adequate ☒ Inadequate

N/A = Not Available.

1 EXECUTIVE SUMMARY

This application contains the results of pivotal fasting and fed bioequivalence (BE) studies comparing a test product, Laurus Labs Limited's Sacubitril and Valsartan Tablets, 97 mg/103 mg, to the corresponding reference standard (RS) product, Novartis Pharmaceuticals Corp's ENTRESTO[®] (sacubitril and valsartan) Tablets, 97 mg/103 mg (NDA 207620, approved on 7/7/2015³). Each of the pivotal BE studies was designed as single-dose, two-treatment, two-sequence, four-period crossover study in healthy male subjects. The applicant's pivotal fasting and fed BE studies are inadequate due to bioanalytical and method validation related deficiencies. The assessor's results are summarized in the tables below.

Sacubitril and Valsartan Tablet 1 × 97 mg/103 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasting Bioequivalence Study No. 662/18							
Sacubitril Unscaled Data							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
AUC _{0-t} (hr.ng/ml)	2842.85	68	2822.45	69	1.01	97.89	103.64
AUC _∞ (hr.ng/ml)	2884.40	68	2894.23	69	1.00	97.10	102.29
C _{max} (ng/ml)	2477.04	68	2486.00	69	1.00	90.51	109.69

Scaled Data								
Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	S ² _{WR}	SWR	Criteria Bound	Method Used	Outcome
LnAUC _{0-t}	1.00	97.89	103.64	0.0087022	0.0932858	-0.004816	Unscaled	PASS
LnAUC _{0-inf}	1.00	97.10	102.29	0.0080885	0.089936	-0.004459	Unscaled	PASS
LnC _{max}	0.98	90.51	109.69	0.1199647	0.3463593	-0.065356	Scaled/PE	PASS

³ Electronic Orange Book,
https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=207620,
 accessed 11/26/2019.

Sacubitril and Valsartan Tablet 1 × 97 mg/103 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasting Bioequivalence Study No. 662/18 Valsartan Unscaled Data							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
AUC _{0-t} (hr.ng/ml)	31909.11	68	35068.25	69	0.91	81.43	101.68
AUC _∞ (hr.ng/ml)	32276.93	68	35419.47	69	0.91	81.68	101.66
C _{max} (ng/ml)	5125.14	68	5727.12	69	0.89	78.93	101.46

Scaled Data								
Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	S ² _{WR}	SWR	Criteria Bound	Method Used	Outcome
LnAUC _{0-t}	0.91	81.43	101.68	0.0668375	0.2585296	-0.005983	Unscaled	PASS
LnAUC _{0-inf}	0.91	81.68	101.66	0.0649223	0.2547985	-0.005902	Unscaled	PASS
LnC _{max}	0.89	78.93	101.46	0.0923752	0.3039329	-0.010139	Scaled/PE	PASS

Sacubitril and Valsartan Tablet 1 × 97 mg/103 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fed Bioequivalence Study No. 663/18 Sacubitril Unscaled Data							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
AUC _{0-t} (hr.ng/ml)	2707.46	55	2658.34	55	1.02	98.99	104.79
AUC _∞ (hr.ng/ml)	2781.48	54	2701.67	55	1.03	100.14	105.85
C _{max} (ng/ml)	1417.07	55	1490.46	55	0.95	83.25	108.59

Scaled Data								
Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	S ² _{WR}	SWR	Criteria Bound	Method Used	Outcome
LnAUC _{0-t}	1.02	98.99	104.79	0.0072154	0.0849436	-0.002731	Unscaled	PASS
LnAUC _{0-inf}	1.03	100.14	105.85	0.007031	0.0838509	-0.001246	Unscaled	PASS
LnC _{max}	0.93	83.25	108.59	0.1046236	0.3234557	-0.031593	Scaled/PE	PASS

Sacubitril and Valsartan Tablet 1 × 97 mg/103 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasting Bioequivalence Study No. 662/18 Valsartan Unscaled Data							

Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
AUC _{0-t} (hr.ng/ml)	23898.80	55	22299.16	55	1.07	100.12	114.73
AUC _∞ (hr.ng/ml)	24223.20	55	22662.43	55	1.07	99.92	114.34
C _{max} (ng/ml)	3101.31	55	2983.30	55	1.04	96.45	112.05

Scaled Data								
Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	S ² _{WR}	SWR	Criteria Bound	Method Used	Outcome
LnAUC _{0-t}	1.08	100.12	114.73	0.0449237	0.211952	-0.010853	Unscaled	PASS
LnAUC _{0-inf}	1.08	99.92	114.34	0.0440856	0.2099657	-0.011334	Unscaled	PASS
LnC _{max}	1.04	96.45	112.05	0.0455111	0.2133333	-0.018156	Unscaled	PASS

Additionally, the applicant submitted data for one pilot fasting and one pilot fed BE studies (Study Nos. 060/18 and 059/18, respectively) comparing the test formulation lot 15140-A-044 to the reference product (Lot # FX000079). According to the applicant's submission, the pilot test formulation 15140-A-044 is the same as the bio lot (Lot # E1801121) used in the pivotal fasting and fed BE studies. The pilot fasting BE study was designed as a single-dose, two-treatment, two-sequence, four-period crossover study in healthy male subjects while the pilot fed BE study was designed as single-dose, two-way crossover study in healthy male subjects. Based on the applicant's results, the pilot fasting and fed BE studies failed to meet the BE acceptance criteria. No deaths or serious adverse events were reported during the pilot BE studies. The applicant's results of the pilot BE studies are summarized below.

Reference Scaled Average Bioequivalence Approach Used						☒ Yes ☐ No		
Sacubitril and Valsartan tablets 97mg/103 mg (No of subjects completed= 20)								
Dose (1 X 97mg/103 mg)								
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals								
Fasting Bioequivalence Study (Study No. 060/18) (Sacubitril)								
Parameter	Test	N	Reference	N	Ratio (%)	90% C.I.		
AUC _t (hr*ng /mL)	5760.197	38	5963.343	40	95.88	92.16 - 101.24		
AUC _{inf} (hr*ng /mL)	5784.173	38	5986.719	40	95.91	92.20 - 101.24		
C _{max} (ng/ml)	4344.789	38	5107.160	40	82.12	74.07 - 97.72		
Fasting Bioequivalence Study (Study No. 060/18) (Valsartan)								
Parameter	Test	N	Reference	N	Ratio (%)	90% C.I.		
AUC _t (hr*ng /mL)	23751.89	38	24305.17	40	96.06	85.54 - 111.64		
AUC _{inf} (hr*ng /mL)	24056.85	38	24626.61	40	96.04	85.66 - 111.41		
C _{max} (ng/ml)	3424.471	38	3719.109	40	90.47	79.85 - 106.18		
Fasting Bioequivalence Study (Study No. 060/18) (Sacubitril)								
Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s _{2wr}	s _{WR}	95% Criteria Bound	Method Used	Outcome
LAUCT	95.88	92.16	101.24	0.015	0.12253	-.003623587	GLM	PASS

LAUCI	95.91	92.20	101.24	0.015	0.12175	-.003576393	GLM	PASS
LCMAX	82.12	74.07	97.72	0.150	0.38758	0.008185886	GLM	FAIL
Fasting Bioequivalence Study (Study No. 060/18) (Valsartan)								
Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	Outcome
LAUCT	96.06	85.54	111.64	0.089	0.29892	-0.033429	GLM	PASS
LAUCI	96.04	85.66	111.41	0.088	0.29620	-0.032934	GLM	PASS
LCMAX	90.47	79.85	106.18	0.082	0.28570	0.001875	GLM	FAIL

Reference Scaled Average Bioequivalence Approach Used						☐ Yes ☒ No	
Sacubitril and Valsartan tablets 97mg/103 mg (No of subjects completed= 14)							
Dose (1 X 97mg/103 mg)							
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fed Bioequivalence Study (Study No. 059/18) (Sacubitril)							
Parameter	Test	N	Reference	N	Ratio (%)	90% C.I.	
AUC _t (hr*ng /mL)	5024.3659	14	5436.0285	14	92.43	87.53- 97.60	
AUC _{inf} (hr*ng /mL)	5255.2521	14	5486.6160	14	95.78	87.83- 104.46	
C _{max} (ng/ml)	2152.9224	14	2774.0681	14	77.61	66.03- 91.21	
Fed Bioequivalence Study (Study No. 059/18) (Valsartan)							
Parameter	Test	N	Reference	N	Ratio (%)	90% C.I.	
AUC _t (hr*ng /mL)	12813.6740	14	13300.0989	14	96.34	87.64 - 105.91	
AUC _{inf} (hr*ng /mL)	13107.4899	14	13549.4819	14	96.74	88.12 - 106.20	
C _{max} (ng/ml)	1610.3807	14	1765.7444	14	91.20	83.43 - 99.70	

There is no USP method for this drug product (b)(4)

(b)(4)

(b)(4)

The applicant conducted comparative dissolution testing using the FDA-recommended dissolution method but at a lower speed (i.e. 50 rpm). The assessor notes that the FDA-recommended dissolution method was revised on 10/24/2019 after submission of the current ANDA. In the applicant's pharmaceutical development report, the applicant conducted dissolution testing on prototype test batches using the FDA-recommended dissolution method (b)(4) selected 50 rpm for its dissolution testing on the exhibit batches. Based on the mean dissolution data, for each strength, both the test and reference products showed (b)(4) dissolution profiles (b)(4) % drug release within 30 minutes). The dissolution method and specification for the quality control purposes will be assessed separately in the biopharmaceutics assessment, which, as of 12/10/2019, is pending. Therefore, the assessment of waiver requests for the lower strengths 24 mg/26 mg and 49 mg/51 mg of the test product is pending and will be completed based on the acceptance of the applicant's proposed dissolution method.

The formulation of the lower strengths 24 mg/26 mg and 49 mg/51 mg of the test product are proportional to that of the 97 mg/103 mg bio strength test product, which underwent in vivo BE testing under fasting and fed conditions. The test product formulations are adequate.

At this time, the Division of Bioequivalence (DBI) **does not grant** the waiver request for *in vivo* BE study requirements for the 24 mg/26 mg and 49 mg/51 mg strengths based on criteria set forth in 21 CFR § 320.22 (d)(2).

In a memorandum regarding Office of Study Integrity and Surveillance (OSIS) inspection of the analytical BE site [redacted] (b)(4)

[redacted] (b)(4) for several ANDAs, including the current ANDA, OSIS determined that an inspection is not warranted at this time for the analytical site⁴. The rationale for this decision was “OSIS inspected the site in February 2018, which falls within the surveillance interval. The inspection was conducted under the following submissions: ANDAs [redacted] (b)(4) [redacted] (b)(4). The final classification for the inspection was No Action Indicated (NAI).”

As of 12/10/2019, the OSIS inspection status of the clinical BE site QPS Bioserve India Pvt., Ltd. [# 6-56/6/1A, Opp: IDPL Factory, Balanagar, Hyderabad-500 037, Telangana, India] for the current ANDA is pending (GDRP task status is “In Progress”⁵). The BE 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 analytical site is complete. Upon completion of the clinical site inspection task by OSIS, the BE assessment team will evaluate the inspection outcome.

The application is **inadequate**.

NOTE TO REGULATORY PROJECT MANAGER (RPM):

Currently, there is OSIS inspection pending for the clinical site.

Per OGD Policy, as of 12/10/2019, there is a Policy Alert regarding the RLD ENTRESTO® (sacubitril and valsartan) Tablets stemming from Citizen Petition (CP) FDA-2019-P-1893. In addition, there is another policy alert regarding multiple drug products containing valsartan stemming from CP FDA-2019-P-2869. It is noted that the scope of this CP includes the current drug product, among other valsartan containing drug products.

No Approval Actions (AP/TA) can be taken prior to contacting Policy Lead and all disciplines can continue communications (CRL, IR/DRL). CC should contact Policy if related to CP.

(b)(4)

⁵ GDRP: ANDA-213676-ORIG-1, Clinical PK/PD Sites, Site: QPS BIOSERVE INDIA PVT. LIMITED. Current Task Status: In Progress, accessed 11/28/2019.

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3 SUBMISSION SUMMARY

3.1 Drug Product Information³

Test Drug Product and Strength(s)	Sacubitril and Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg
Reference Standard (RS) and Strength(s)	ENTRESTO® (sacubitril and valsartan) Tablets, 97 mg/103 mg
RS Holder; NDA/ANDA Number; Approval Date	Novartis Pharmaceuticals Corp; NDA 207620; 7/7/2015
Reference Listed Drug (RLD) and Strength(s)	ENTRESTO® (sacubitril and valsartan) Tablets, 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg
RLD Holder; NDA/ANDA Number; Approval Date	Same as the RS

3.2 PK/PD Information⁶

Most recent RLD labeling	 RLD Labeling.pdf
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	WARNING: FETAL TOXICITY - 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 ≥ 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.

⁶ Drugs@FDA: RLD Labeling: Search by Keyword "207620", https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/207620s013lbl.pdf, accessed 11/12/2019.

Food Effect	ENTRESTO administration with food has no clinically significant effect on the systemic exposures of sacubitril, LBQ657, or valsartan. Although there is a 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.
T_{max}	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	Adults and Pediatric 50 kg or more: Sacubitril: 194 mg/day; Valsartan: 206 mg/day Pediatric 40 to 49 kg: Sacubitril: 144 mg/day; Valsartan: 156 mg/day Pediatric less than 40 kg: 3.1 mg/kg (combined amount of Sacubitril and Valsartan twice daily or 248 mg/day combined Sacubitril and Valsartan , resulting in 1 × 97/103 tablet and 1 × 24/26 tablet per day)

3.3 OGD Recommendations for Drug Product

Source of most recent recommendations	Product-Specific Guidance on Sacubitril and Valsartan Tablets (Recommended Apr 2016) https://www.accessdata.fda.gov/drugsatfda_docs/psg/Sacubitril%20Valsartan%20oral%20tablet%20RLD%20207620%20RC04-16.pdf	
Summary of OGD or DB History	Approved ANDAs:	No ⁷

⁷ Electronic Orange Book, search by keyword “Sacubitril and Valsartan”, accessed 11/12/2019.

	Pending ANDAs:	Yes⁸ (b)(4) ANDA 213604 (Pending Assessment) ANDA 213605 (Pending Assessment) ANDA 213611 (Pending Assessment) ANDA 213627 (Pending Assessment) (b)(4) (b)(4) ANDA 213668 (Pending Assessment) (b)(4) ANDA 213676 (Current ANDA) ANDA 213680 (Pending Assessment) ANDA 213682 (Pending Assessment) (b)(4) ANDA 213719 (Pending Assessment) ANDA 213728 (Pending Assessment) ANDA 213748 (Pending Assessment) ANDA 213764 (Pending Assessment) ANDA 213808 (Pending Assessment) (b)(4)
	Controls:	Yes⁹ Multiple, including Controls # 22381167 and 25640141 from the current applicant.
	Protocols:	No¹⁰
	Pending Citizen Petitions and other legal and regulatory issues: ¹¹	☒ Yes ☐ No

Control 22381167¹²:

- The current applicant submitted Control 22381167 proposing to (b)(4)
- (b)(4)

⁸ DARRTS: ANDA Application Search. Keyword “Sacubitril and Valsartan”. ANDA’s most recent status was also verified in GDRP, accessed 11/12/2019.

⁹ GDRP Controls Project Search: search by keyword “Sacubitril and Valsartan”, accessed 11/12/2019. Due to technical issues as of 11/12/2019, a search using OGD Division of Bioequivalence Controls Documents Tracking was not performed

¹⁰ OGD Division of Bioequivalence Protocol Database, accessed 11/12/2019; GDRP: search by keyword “Sacubitril and Valsartan”, accessed 11/12/2019.

¹¹ OGD Policy Alert List as of 11/25/2019, <http://sharepoint.fda.gov/orgs/CDER-OGD/OGDP/OGDPAL/SitePages/Home.aspx>; Regulations.gov, search by keywords “Sacubitril and Valsartan”, accessed 11/26/2019.

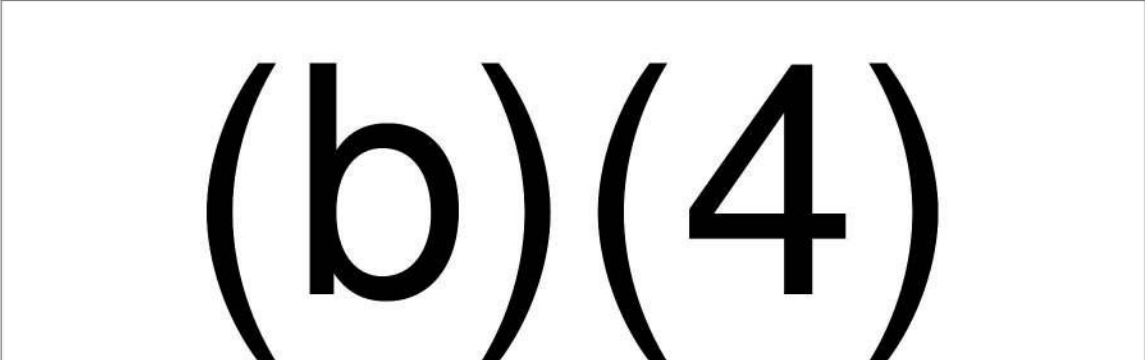
¹² GDRP: Project No. 22381167, Controlled Correspondence: Sacubitril and Valsartan Tablets 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg, RLD N207620-Consideration for an ANDA or NDA [505 (b)(2)]

(b)(4)

mg/51 mg and 97 mg/103 mg in lieu of the pre-formed ionic complex described in the RLD labeling for ENTRESTO® (sacubitril and valsartan) Tablets, 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg. The applicant also wanted to know whether their proposed drug product can be filed as an ANDA or NDA [505 (b)(2)]. The Agency provided the following response to the applicant¹³:

“For a proposed generic drug product of ENTRESTO, it would not be required to be formulated as an anionic complex. The individual drug substances, Sacubitril and Valsartan, can be used in the formulation. However, in order to meet the requirements for pharmaceutical equivalence for a generic drug product as defined in 21 CFR 320.1, the product must contain the same API and the same salt form. In other words, in order to file a 505(j) submission, the same salt form (sodium salts) of the Sacubitril and Valsartan would be required to be used. Therefore, you could file your application as an ANDA as long as you use the mixture with the same ratio of sacubitril: valsartan: sodium cations as in the RLD. Be advised, however, that it is your responsibility to show that the bioavailability and bioequivalence of your drug product are in line with the RLD if you choose not to formulate using the anionic complex.”

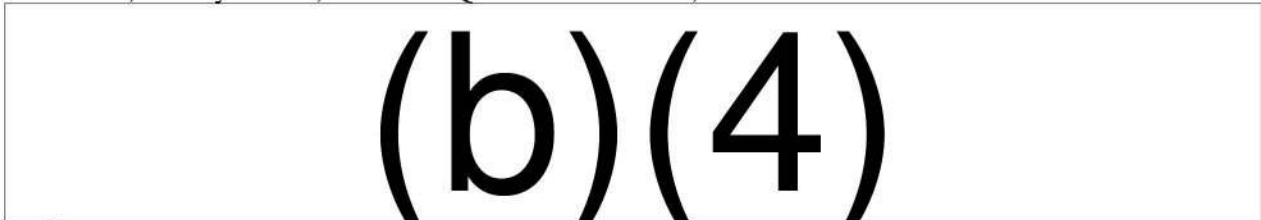
Control 25640141¹⁴:

• 

Policy Alert¹¹:

- As of 11/25/2019, there is a Policy Alert regarding the RLD ENTRESTO® (sacubitril and valsartan) Tablets stemming from CP FDA-2019-P-1893¹⁶. In

¹³ GDRP: Project No. 22381167, Controlled Correspondence: Sacubitril and Valsartan Tablets 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg, RLD N207620-Consideration for an ANDA or NDA [505 (b)(2)] Application by using individual APIs and not a complex of APIs in the Drug Product Formula, OPQ Review, Primary Review, C22381167QLTYReview01.docx, 5/30/2018.



¹⁶ The petitioner of CP FDA-2019-P-1893 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

addition, there is another policy alert regarding multiple drug products containing valsartan stemming from CP FDA-2019-P-2869¹⁷. It is noted that the scope of this CP includes the current drug product, among other valsartan containing drug products. For both policy alerts, no Approval Actions (AP/TA) can be taken prior to contacting Policy Lead and all disciplines can continue communications (CRL, IR/DRL). CC should contact Policy if related to CP.

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 [Regulations.gov: <https://www.regulations.gov/contentStreamer?documentId=FDA-2019-P-1893-0001&attachmentNumber=1&contentType=pdf>, accessed 11/18/2019.].

¹⁷ The petitioner of CP FDA-2019-P-2869 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 [Regulations.gov: <https://www.regulations.gov/contentStreamer?documentId=FDA-2019-P-2869-0001&attachmentNumber=1&contentType=pdf>, accessed 11/18/2019.].

3.4 Pre-Study Bioanalytical Method Validation

Information Requested	Data	
Bioanalytical method validation report location	Module 5, 5.3.1.4, Appendix 16.6, Method Validation Report – page 01 of 111 to 111 of 111	
Analyte	Sacubitril and Valsartan	
Internal standard (IS)	Sacubitril 13C4 and Valsartan –D9	
Method description	(b) (4)	
Limit of quantitation	Valsartan	Sacubitril
	16.769 ng/mL	20.084 ng/mL
Recovery of drug at each QC (%CV)	Avg.: 92.2% (3.2%) HQC: 92.41% MQC: 89.10% LQC: 95.04%	Avg.: 87.6% (1.3%) HQC: 87.96% MQC: 86.38% LQC: 88.54%
Average recovery of IS (%)	96.2%	91.9%
Standard curve concentrations (ng/mL)	16.769, 33.538, 83.845, 201.07, 502.66, 1305.6, 3008.3, 6016.7, 9020.5, and 10023	20.084, 40.169, 100.42, 240.82, 602.05, 1563.8, 3603.1, 7206.3, 10804, and 12004
QC concentrations (ng/mL)	LLOQ QC: 16.810 LQC : 48.443 AQC-II: 403.69 AQC-I: 1106.0 MQC: 3511.1 HQC: 7616.3	LLOQ QC: 20.131 LQC : 58.014 AQC-II: 483.45 AQC-I: 1324.5 MQC: 4204.9 HQC: 9121.2
QC Intraday precision range (%)	0.9% to 2.9%	0.6% to 3.0%
QC Intraday accuracy range (%)	96.6% to 103.2%	95.9% to 101.0%
QC Interday precision range (%)	1.5% to 2.5%	1.3% to 2.1%
QC Interday accuracy range (%)	97.3% to 102.4%	97.2% to 100.5%
Bench-top stability (hrs)	18 hrs @ bench top (room temperature) condition	
Stock stability (days)	23 days @ -20°C ± 10°C	
Processed stability (hrs)	74 hrs @ auto sampler temperature (5°C)	
Freeze-thaw stability (cycles)	Five Cycles @ -20°C ± 10°C and -70°C ± 15°C	
Long-term storage stability (days)	154 days @ -20°C ± 10°C and -70°C ± 15°C	
Dilution integrity	20043 ng/mL, diluted 2 and 5 fold Valsartan	

	(2 Fold: Accuracy = 97.4%; %CV = 1.3%) (5 Fold: Accuracy = 100.2%; %CV = 1.8%) Sacubitril (2 Fold: Accuracy = 100.5%; %CV = 1.5%) (5 Fold: Accuracy = 99.1%; %CV = 1.0%)
Selectivity	No interference peaks noted in blank plasma samples

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
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
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: Incomplete

- The applicant submitted two pre-study method validation reports for each of the pivotal fasting and fed BE studies. The two reports are identical. Method validation and its supplement reports included in the pivotal fasting BE study were used to verify the pre-study method validation information for the above table.
- K₂EDTA was used as an anticoagulant in the pre-study method validation. Calibrators and quality controls (QCs) were prepared in screened pooled blank human plasma containing K₂EDTA, the same anti-coagulant used during in-study subject sample analysis.
- The applicant submitted SOP for bioanalytical method validation, SOP (b)(4) "Bioanalytical Method Validation", which was effective on (b)(4) before the start of original method validation experiments in November 2018. The assessor verified that the pre-study method validation experiments for valsartan and sacubitril were performed in line with the SOP.
- According to the method validation report, the applicant conducted three (3) partial method validations (PMVs). The date and purpose of PMVs applicable to the current BE study are summarized below.

Addendum No.	Date	Reason
I	08/04/2019	Long-term storage stability in matrix for the quantification of Valsartan and Sacubitril in K ₂ EDTA human plasma.

Addendum No.	Date	Reason
II	23/04/2019	Stock Solution Stability at Freezer (-20°C ± 10°C) condition of Valsartan and Sacubitril
III	23/05/2019	Long term storage stability and OTC and Concomitant medications interference test for the quantification of Valsartan and Sacubitril in K ₂ EDTA human plasma

- Per the applicant's bioanalytical reports for the fasting and fed BE studies, the study samples contain valsartan and sacubitril. Per RLD labeling, following drug product administration, sacubitril is converted to the active metabolite LBQ657, which would also be found in the study plasma samples. During the method validation and sample analysis for valsartan and sacubitril, calibration curve standards (CCs) and QC samples were prepared by spiking K₂EDTA plasma with methanolic working solution containing valsartan and sacubitril only, which is not reflective of the study samples composition. It is noted that the applicant did not conduct cross-validation study to evaluate the interference of LBQ657 on the analysis of valsartan and sacubitril. The assessor checked other in house ANDAs for the same drug product and found that analytical method used to analyze valsartan and sacubitril was validated using QCs containing LBQ657 (b)(4). (b)(4) Therefore, at this time, the assessor finds the composition of CCs and QCs for valsartan and sacubitril not acceptable. The applicant will be asked to provide method validation data evaluating the impact of LBQ657 on the analysis of valsartan and sacubitril. The applicant will be also asked to demonstrate the stability of valsartan and sacubitril in the presence of LBQ657.
- The long-term storage stability (LTSS) testing of 154 days at -20°C ± 10°C and -70°C ± 15°C exceeds the maximum sample storage duration of 51 days and 50 days in the pivotal fasting and fed BE studies, respectively, at -20°C ± 10°C at the clinical and analytical sites.

The pre-study method validation is **incomplete**.

(b) (4)

3.5 In Vivo Studies

Summary of all in vivo Bioequivalence Studies

Pivotal Fasting BE Study (Study No. 662/18)

Sacubitril

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range))	Mean Parameters $\pm$ SD (%CV) for Sacubitril						Study Report Location
					C_{max} (ng/mL)	T_{max} (hr) Median (Range)	AUC_t (hr*ng/mL)	AUC_{inf} (hr*ng/mL)	$t_{1/2}$ (hr)	k_{el} (hr ⁻¹)	
662/18	To assess the bioequivalence of Sacubitril and Valsartan tablets 97mg/103 mg of Laurus Labs Limited, India comparing with that of ENTRESTO™ (sacubitril / valsartan) tablets 97mg/103 mg of Novartis Pharmaceuticals Corp East Hanover, NJ 07936 in healthy, adult, human subjects under fasting conditions. To monitor adverse events and ensure the safety and tolerability of subjects	An open label, balanced, two-randomized, two-treatment, four-period, two-sequence, single dose, crossover, full-replicate, oral bioequivalence study in healthy, adult, human subjects under fasting conditions.	Test product (T): 01 tablet Sacubitril and Valsartan tablets 97mg/103 mg Administered orally Batch No. E1801121 Reference product (R): 01 tablet ENTRESTO™ (sacubitril / valsartan) tablets 97mg/103 mg Administered orally Lot Number: FX000079	35 Healthy, adult, male, human subjects Age: 31.5 (22.0 – 42.0)	2764.3 $\pm$ 1168.5 (42.271)	0.67 (0.25 – 4.00)	2957.842 $\pm$ 746.195 (25.228)	3000.938 $\pm$ 752.362 (25.071)	0.71 $\pm$ 0.24 (33.72)	1.0598 $\pm$ 0.2886 (27.2297)	This information has been extracted from the Clinical Study Report (Pages 97 of 213 and 101 of 213)
					2718.4 $\pm$ 1129.8 (41.561)	0.67 (0.25 – 2.67)	2948.846 $\pm$ 765.588 (25.962)	3014.050 $\pm$ 738.086 (24.488)	0.72 $\pm$ 0.23 (31.97)	1.0512 $\pm$ 0.3049 (29.0036)	

Valsartan

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range))	Mean Parameters $\pm$ SD (%CV) for Valsartan						Study Report Location
					C_{max} (ng/mL)	T_{max} (hr) Median (Range)	AUC_t (hr*ng/mL)	AUC_{inf} (hr*ng/mL)	$t_{1/2}$ (hr)	k_{el} (hr ⁻¹)	
662/18	To assess the bioequivalence of Sacubitril and Valsartan tablets 97mg/103 mg of Laurus Labs Limited, India comparing with that of ENTRESTO™ (sacubitril / valsartan) tablets 97mg/103 mg of Novartis Pharmaceuticals Corp East Hanover, NJ 07936 in healthy, adult, human subjects under fasting conditions. To monitor adverse events and ensure the safety and tolerability of subjects	An open label, balanced, randomized, two-treatment, four-period, two-sequence, single dose, crossover, full-replicate, oral bioequivalence study in healthy, adult, human subjects under fasting conditions.	Test product (T): 01 tablet Sacubitril and Valsartan tablets 97mg/103 mg Administered orally Batch No. E1801121 Reference product (R): 01 tablet ENTRESTO™ (sacubitril / valsartan) tablets 97mg/103 mg Administered orally Lot Number: FX000079	35 Healthy, adult, male, human subjects Age: 31.5 (22.0 – 42.0)	5739.4 $\pm$ 2358.5 (41.093)	2.00 – (1.00 – 4.50)	35830.293 $\pm$ 14731.981 (41.116)	36146.871 $\pm$ 14745.770 (40.794)	6.91 $\pm$ 1.58 (22.80)	0.1058 $\pm$ 0.0257 (24.3360)	This information has been extracted from the Clinical Study Report (Pages 153 of 213 and 157 of 213)
					6208.7 $\pm$ 2219.9 (35.754)	2.00 – (1.00 – 4.00)	38176.360 $\pm$ 14148.166 (37.060)	38511.136 $\pm$ 14185.715 (36.835)	6.79 $\pm$ 1.63 (24.04)	0.1077 $\pm$ 0.0245 (22.7380)	

Pivotal Fed BE Study (Study No. 663/18)

Sacubitril

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range))	Mean Parameters +/-SD (%CV) for Sacubitril						Study Report Location
					C _{max} (ng/mL)	T _{max} (hr) Median (Range)	AUC _t (hr*ng/mL)	AUC _{inf} (hr*ng/mL)	t _{1/2} (hr)	k _{el} (hr ⁻¹)	
663/18	To assess the bioequivalence of Sacubitril and Valsartan tablets 97mg/103 mg of Laurus Labs Limited, India comparing with that of ENTRESTO™ (sacubitril / valsartan) tablets 97mg/103 mg of Novartis Pharmaceuticals Corp East Hanover, NJ 07936 in healthy, adult, human subjects under fed conditions. To monitor adverse events and ensure the safety and tolerability of subjects	An open label, balanced, randomized, two-treatment, four-period, two-sequence, single dose, crossover, full-replicate, oral bioequivalence study in healthy, adult, human subjects under fed conditions.	Test product (T): 01 tablet Sacubitril and Valsartan tablets 97mg/103 mg Administered orally Batch No. E1801121 Reference product (R): 01 tablet ENTRESTO™ (sacubitril / valsartan) tablets 97mg/103 mg Administered orally Lot Number: FX000079	28 Healthy, adult, male, human subjects Age: 31.2 (22.0 – 44.0)	1541.1 ± (40.318)	1.67 (0.50 – 10.00)	2750.097 ± (17.476)	2820.276 ± (18.227)	1.12 ± (81.36)	0.8407 ± (42.9511)	This information has been extracted from the Clinical Study Report (Pages 90 of 186 and 93 of 186)
					1617.5 ± (41.510)	1.67 (0.67 – 4.50)	2709.062 ± (19.911)	2755.351 ± (20.523)	1.01 ± (133.91)	0.9431 ± (34.4506)	

Valsartan

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range))	Mean Parameters $\pm$ SD (%CV) for Valsartan						Study Report Location
					C_{max} (ng/mL)	T_{max} (hr) Median (Range)	AUC_t (hr $\cdot$ ng/mL)	AUC_{inf} (hr $\cdot$ ng/mL)	$t_{1/2}$ (hr)	k_{el} (hr $^{-1}$)	
663/18	To assess the bioequivalence of Sacubitril and Valsartan tablets 97mg/103 mg of Laurus Labs Limited, India comparing with that of ENTRESTO™ (sacubitril / valsartan) tablets 97mg/103 mg of Novartis Pharmaceuticals Corp East Hanover, NJ 07936 in healthy, adult, human subjects under fed conditions.	An open label, balanced, randomized, two-treatment, four-period, two-sequence, single dose, crossover, full-replicate, oral bioequivalence study in healthy, adult, human subjects under fed conditions.	Test product (T): 01 tablet Sacubitril and Valsartan tablets 97mg/103 mg Administered orally Batch No. E1801121	28 Healthy, adult, human subjects	3203.4 $\pm$ 800.88 (25.001)	3.67 (1.33 – 12.00)	24826.137 $\pm$ 7185.497 (28.943)	25142.183 $\pm$ 7206.491 (28.663)	7.22 $\pm$ 1.53 (21.20)	0.1004 $\pm$ 0.0219 (21.7965)	This information has been extracted from the Clinical Study Report (Pages 136 of 186 and 139 of 186)
			Reference product (R): 01 tablet ENTRESTO™ (sacubitril / valsartan) tablets 97mg/103 mg Administered orally Lot Number: FX000079		3100.0 $\pm$ 836.64 (26.988)	3.33 (1.33 – 5.00)	23284.823 $\pm$ 6740.792 (28.949)	23635.315 $\pm$ 6729.574 (28.473)	7.20 $\pm$ 1.77 (24.62)	0.1015 $\pm$ 0.0229 (22.5795)	
	To monitor adverse events and ensure the safety and tolerability of subjects										

4 APPENDIX

4.1 Individual Study Assessments

4.1.1 Single-Dose Pivotal Fasting Bioequivalence Study

4.1.1.1 Study Design

4.1.1.1.1 Study Information

Study Number	662/18	
Study Title	An open label, balanced, randomized, two-treatment, four-period, two-sequence, single dose, crossover, full-replicate, oral bioequivalence study of Sacubitril and Valsartan tablets 97 mg/103 mg of Laurus Labs Limited, India comparing with ENTRESTO™ (sacubitril/valsartan) tablets 97 mg/103 mg of Novartis Pharmaceuticals Corp East Hanover, NJ 07936 in healthy, adult, human subjects under fasting conditions	
Clinical Site (Name & Address)	QPS Bioserve India Pvt. Limited, # 6-56/6/1A, Opp: IDPL Factory, Balanagar, Hyderabad-500 037, Telangana, India. Tel: +91-40-4377 0873 / 1875 Fax: +91-40-4377 0877	
Principal Clinical Investigator	Dr. K.Babji babji.kalmanoor @qpsbioserve.com	
Dosing Dates	Period I: 19/02/2019 Period II: 26/02/2019 Period III: 05/03/2019 Period IV: 12/03/2019	
Analytical Site (Name & Address)	(b)(4)	
Analysis Dates	14/03/2019-10/04/2019	
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)	(19/02/2019 to 10/04/2019) 51 days -20°C ± 10°C	
Long-Term Storage Stability (LTSS) Coverage (no. days @ temp °C)	154 days @ -20°C ± 10°C and -70° ± 15°C	

4.1.1.1.2 Product (Bio-batch) Information

Product	Test	RLD
Treatment ID	T	R
Product Name	Sacubitril and Valsartan tablets 97 mg/103 mg	ENTRESTO™ (sacubitril / valsartan) tablets 97 mg/103 mg
Manufacturer	Laurus Labs Limited, India	(b)(4)
Batch/Lot No.	E1801121*	FX000079
Manufacture Date	Dec-2018	
Expiration Date		Jul 2020
Strength	97 mg/103 mg	97 mg/103 mg
Dosage Form	Tablet	Tablet
Bio-Batch Size	(b)(4)	
Production Batch Size		
Potency (Assay)	Sacubitril 101.7% Valsartan 102.1 %	Sacubitril 99.5% Valsartan 99.1%
Content Uniformity (expressed as mean, %CV or per USP)	Sacubitril Acceptance Value: 2.4 Valsartan Acceptance Value: 2.6	
Dose Administered	1 × 97 mg/103 mg	1 × 97 mg/103 mg
Route of Administration	Oral	Oral

* Assessor's note: Lot no. E1801121 used in the BE study is for the finished product packaged (b)(4) Bottle Pack of 30 tablets²⁰. The lot no. for the unpackaged finished product is E180112.

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 ☐ No

²⁰ GS Review: ANDA 213676, New/ANDA, 07/08/2019 (Module 3.2.R. Yield and Reconciliation - Drug Product.pdf).

Assessor's Comments:

- The Certificate of Analysis (CoA) for the RLD product ENTRESTO® (sacubitril and valsartan) Tablets, 97 mg/103 mg, indicates that the RLD product was manufactured (b)(4). The RLD labeling does not contain information on the U.S. manufacturer of the RLD product but only the distributor (Novartis Pharmaceuticals Corporation East Hanover, New Jersey)⁶. (b)(4)
(b)(4)
(b)(4). Therefore, the assessor finds that the RLD batch used in the pivotal fasting and fed BE studies was manufactured for the United States market and thus acceptable.

4.1.1.1.3 Study Design, Single-Dose Pivotal Fasting Bioequivalence Study

Number of Subjects	Enrolled: 36 Dosed: 36 Completed: 35 completed at least 2 periods and 33 completed all periods Samples Analyzed: 36 Statistically Analyzed: 35
No. of Sequences	2
No. of Periods	4
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization	☒ Yes ☐ No
Blood Sampling Times	Blood samples were collected at pre-dose (0.00) and 0.08, 0.17, 0.25, 0.33, 0.50, 0.67, 0.83, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00, 36.00 and 48.00 hours post dose.
IRB Approval	☒ Yes Date: 24/12/2018 ☐ No
Informed Consent	☒ Yes Date: 24/12/2018 ☐ No
Length of Fasting	An overnight fast of at least 10 hours prior to drug administration and at least 4 hours post-dose.
Length of Confinement	At least 11 hours prior to dosing until 48.00 hours post-drug administration.
Was the drug product administered per labeling for specialized dosage forms e.g. ODT?	☐ Yes ☐ No ☒ N/A
Safety Monitoring	☒ Yes ☐ No

(b)(4)

Comments on Study Design: Adequate

- The study design for the pivotal fasting BE study (Study No. 662/18) was an open label, single-dose, randomized, two-treatment, four-period, two-sequence, full-replicate, crossover BE study, which is not in line with the recommendation in the product-specific guidance (PSG) for Sacubitril and Valsartan Tablets, 97 mg/103 mg. The applicant did not provide an explanation for its selected BE study design. It is noted that the applicant conducted pilot fasting BE study (Study No. 060/18) as recommended in the PSG (i.e. single-dose, two-way crossover study), which failed to meet the BE acceptance limits possibly due to high intra-subject variability observed during the pilot BE study under fasting condition. The assessor deems the applicant's BE study design acceptable for the following reasons:
 - 1) The applicant's pilot fasting BE study conducted per PSG recommendation failed to meet the BE limit for C_{max} for sacubitril and valsartan presumably due to highly intra-subject variability.
 - 2) The applicant has pre-established the fully-replicate study design prior to conducting the pivotal fasting BE study.
 - 3) In Office for Research and Standards (ORS)'s responses to Controlled Correspondence no. 23610606²² and no. 24442067²³ for the same drug product, ORS concluded that a fully replicated crossover BE study design under fasting conditions is acceptable for the current drug product provided that the applicant provides evidence of high variability (i.e. $SWR \geq 0.294$) in the pharmacokinetic parameters (C_{max} and/or AUC) of the reference product. In the current pivotal fasting BE study, SWR value for C_{max} for sacubitril and valsartan was ≥ 0.294 . Therefore, the applicant used the reference-scaled average approach to demonstrate BE for C_{max} and the conventional two one-sided test procedure to demonstrate BE for AUC_{0-t} and $AUC_{0-\infty}$.
- Per RLD labeling⁶, following oral administration, the peak plasma concentrations for sacubitril and valsartan occurred between 0.5 and 1.5 hours, respectively. In addition, sacubitril and valsartan have terminal elimination half-lives of approximately 1.4 and 9.9 hours, respectively. The applicant collected blood samples up to 48 hours post-dose, which is adequate to capture the T_{max} and elimination phase with no first time point C_{max} observed. The washout period of 7 days between study periods is more than five half-lives of sacubitril and valsartan and thus is sufficient to ensure the complete elimination of remaining sacubitril and valsartan before the next dosing period.

²² GDRP: Project No. 23610606, Controlled Correspondence: Sacubitril and Valsartan Tablet, 97 mg;103mg [RLDN207620] - Confirmation on study design of bioequivalence study, OGD Review, C23610606 Review.docx, 9/27/2018.

²³ GDRP: Project No. 24442067, Controlled Correspondence: Sacubitril and Valsartan Tablets, 97mg;103mg - for Alternative Approach and Design of Bioequivalence (BE) Study RLD#207620, OGD Review, C24442067 Review.docx, 10/26/2018.

- The current PSG on Sacubitril and Valsartan Tablets, 97 mg/103 mg recommends that fasting BE study be conducted in *[h]ealthy males and females (nonpregnant), general population. Female subjects should not be pregnant or lactating, and if applicable, should practice abstinence or contraception during the study.* Per clinical study report, the pivotal fasting BE study was conducted in male subjects only and thus in line with the recommendations in the current PSG.

The pivotal fasting BE study design is **adequate**.

4.1.1.2 Clinical Results

4.1.1.2.1 Demographic Profile of Subjects

Pivotal Fasting Bioequivalence Study No. 662/18			
		Treatment Groups	
		Test Product N = 35	Reference Product N = 35
Age (years)	Mean ± SD	31.5 ± 6.9	31.5 ± 6.9
	Range	22.0 - 42.0	22.0 - 42.0
Age Groups	< 18	0 (0.00%)	0 (0.00%)
	18 – 40	30 (85.71%)	30 (85.71%)
	41 – 64	05 (14.29%)	05 (14.29%)
	65 – 75	0 (0.00%)	0 (0.00%)
	> 75	0 (0.00%)	0 (0.00%)
Sex	Male	35 (100%)	35 (100%)
	Female	0 (0.00%)	0 (0.00%)
Race	Asian	35 (100%)	35 (100%)
	Black	0 (0.00%)	0 (0.00%)
	Caucasian	0 (0.00%)	0 (0.00%)
	Hispanic	0 (0.00%)	0 (0.00%)
	Other	0 (0.00%)	0 (0.00%)
BMI	Mean ± SD	23.2 ± 1.7	23.2 ± 1.7
	Range	19.0 - 24.9	19.0 - 24.9
Other Factors		NA	NA

NA = Not Applicable

Is the demographics profile of subjects completing the bioequivalence study in agreement with the current drug product recommendation? If no, please comment.	☒ Yes ☐ No

4.1.1.2.2 Dropout Information

Subject No.	Reason	Period	Replaced?

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(b)(6)	Subject did not turn up for period-II and period-III check-in due to personal reasons	II & III	No
	Subject did not turn up for period-III check-in due to personal reasons	III	No
	Subject did not turn up for period-II, period-III and period-IV check-in due to personal reasons	II, III & IV	No

Are dropouts appropriate? If no, please comment.	☒ Yes ☐ No ☐ N/A

4.1.1.2.3 Study Adverse Events

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Pivotal Fasting Bioequivalence Study No. 662/18	
	Test (N = 35)	Reference (N = 36)
Gastrointestinal disorders		
Diarrhea	02 (5.71%)	-
Respiratory, thoracic and mediastinal disorders		
Dry cough	01 (2.86%)	03 (8.33%)
Skin and subcutaneous tissue disorders		
Itching all over body	02 (5.71%)	01 (2.78%)
Rashes over body	01 (2.86%)	01 (2.78%)
Nervous system disorders		
Dizziness	01 (2.86%)	-
Headache	01 (2.86%)	01 (2.78%)
Total	08 (22.86%)	06 (16.67%)

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 T_{max} 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 ☐ N/A (see comment below)
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/CSSS via the OGD-PremarketSafetyReports@fda.hhs.gov mailbox?	☐ 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

Type	Subject #s (Test T)	Subject #s (Reference R)
In House Blood Draw deviation	Period-IV	
	(b)(6) (1.33 hr)	-

If the applicant 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

- A total of 36 subjects were enrolled and dosed in the pivotal fasting BE study. Per clinical study report, Subject (b)(6) did not report to the clinical facility for periods II and III check-in, subject (b)(6) did not report to the clinical facility for period III check-in, and subject (b)(6) did not report to the clinical facility for period II-IV check-in due to personal reasons. The assessor checked the study protocol and Case Report Forms (CRFs) for the above subjects and verified that Subjects (b)(6) returned for period IV following discontinuation from periods II-III (Subject (b)(6) and period III (Subject (b)(6)) and the withdrawal of Subject (b)(6) was in line with the study protocol and no plasma samples were collected following the discontinuation/dropout. The collected samples from the discontinued subjects were analyzed but only Subjects (b)(6) were considered for pharmacokinetic and statistical analyses with the remaining subjects since they completed at least 2 study periods, which is in line with the study protocol.
- Per the clinical study report, 14 adverse events (AEs) were reported following the administration of the test and reference products in all study periods I-IV. Most of these AEs are listed in the RLD labeling. Per the clinical study report and CRFs, the reported AEs were considered to be mild or moderate and possibly or unlikely related to the study treatment. These AEs were resolved by the end of study without any sequelae. Based on the number of observed AEs, the AE profile are not comparable between test and reference. However, since the majority of AEs are single incidence and the subjects who had these AEs did not have any other complaints upon check-out, the assessor does not consider the above reported AEs would impact the BE study outcome.
- According to the clinical study report, Subjects (b)(6) received the following concomitant medications orally: Cetirizine Hydrochloride Tablets, Lactic Acid Bacillus Tablets, Paracetamol Tablets, TusQ-X + (Terbutaline Sulphate, Ambroxol Hydrochloride and Guaifenesin) Syrup. In addition, Subjects (b)(6) received the following concomitant medication intravenously: Pheniramine Maleate 22.75 mg Injection. The applicant's pre-study method

validation includes the evaluation of aforementioned concomitant medications except Lactic Acid Bacillus, which was administered to Subject (b)(6) who suffered from diarrhea. However, Subject (b)(6) received Lactic Acid Bacillus 33 hours and 33 minutes after drug administration, and Subject (b)(6)'s C_{max} for valsartan and sacubitril was observed at 0.5 and 1.67 hours, respectively. Therefore, since Lactic Acid Bacillus was administered in the elimination phase of Subject (b)(6), this concomitant medication should not significantly affect the BE study outcome. Per the pre-study method validation report, the applicant demonstrated that the aforementioned concomitant medications do not interfere with the analytical measurement of valsartan and sacubitril. Therefore, the assessor does not consider these concomitant medications will impact the study outcome.

- The applicant reported one protocol deviation of In House Blood Draw deviation for Subject (b)(6) as the sampling collection time at 1.33 hour time point was deviated by 4 minutes due to cannula blockage. According to the clinical study report, the applicant used actual blood sampling time points for the calculation of pharmacokinetic parameters. The assessor also used actual blood sampling time points. Therefore, the assessor does not consider this protocol deviation would affect the calculation of pharmacokinetic parameters and the study outcome.

The handling of adverse events, dropouts, and protocol deviations is **acceptable**.

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)		Reanalysis of Study Samples
		Preparation and Qualification of Calibration Curve Standards and Quality Control Samples
		Bioanalytical Method Validation
		Chromatogram Acceptance Criteria
		Biosample Analysis and Within Study Validation
		Incurred Sample Reanalysis
		Quantification of Valsartan and Sacubitril

All necessary SOPs submitted?	☒ Yes ☐ No

4.1.1.3.2 Sample Analysis Calibration and Quality Control

Pivotal Fasting Bioequivalence Study No. 662/18 Sacubitril	
Parameter	Standard Curve Samples

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Concentration (ng/mL)	20.124	40.249	100.62	240.15	600.37	1563.5	3602.5	7204.9	10802	12002
Inter day Precision (%CV)	1.5	2.6	2.1	1.6	1.6	1.7	1.9	1.6	2.7	1.8
Inter day Accuracy (%Actual)	98.7	101.0	102.1	103.1	102.7	102.5	100.3	97.9	95.3	96.2
Linearity (R ²)	0.9962 to 0.9994									
Linearity Range (ng/mL)	20.124 to 12002									
Sensitivity/LOQ (ng/mL)	20.124									

Parameter	Quality Control Samples				
	HQC	MQC	AQC-I	AQC-II	LQC
Concentration (ng/mL)	9120.3	4204.4	1324.4	483.41	58.009
Inter day Precision (%CV)	2.1	1.8	2.5	2.4	2.9
Inter day Accuracy (%Actual)	97.4	101.2	103.5	103.9	103.3

Pivotal Fasting Bioequivalence Study No. 662/18 Valsartan										
Parameter	Standard Curve Samples									
	Concentration (ng/mL)	16.804	33.607	84.019	200.52	501.31	1305.5	3008.0	6016.0	9019.6
Inter day Precision (%CV)	1.5	2.9	2.3	1.8	2.5	1.9	2.3	1.8	3.3	2.7
Inter day Accuracy (%Actual)	99.5	100.6	100.1	101.1	100.6	101.0	99.7	99.8	97.4	100.1
Linearity (R ²)	0.9966 to 0.9998									
Linearity Range (ng/mL)	16.804 to 10022									
Sensitivity/LOQ (ng/mL)	16.804									

Parameter	Quality Control Samples				
	HQC	MQC	AQC-I	AQC-II	LQC
Concentration (ng/mL)	7615.3	3510.7	1105.9	403.64	48.437
Inter day Precision (%CV)	2.8	2.3	2.8	2.6	3.9
Inter day Accuracy (%Actual)	99.4	100.9	102.4	102.4	102.4

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	☒ Yes ☐ No
Are there any concerns related to sample analysis (including rejected runs, reinjection, sample dilution, etc.)? If yes, comment below or consult TL/tertiary assessor for additional actions	☐ Yes ☒ No
Were 20% of chromatograms included?	☒ Yes ☐ No
Were chromatograms serially or randomly selected?	☒ serially ☐ randomly (Subjects (b)(6))
Any interfering peaks in chromatograms?	☐ Yes ☒ No
Were the chromatograms submitted by the applicant acceptable?	☒ Yes ☐ No
Were 100% raw analytical data, including failed runs, provided?	☒ Yes ☐ No

4.1.1.3.3 Reanalysis of Study Samples

Pivotal Fasting Bioequivalence Study No. 662/18 Sacubitril								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used in reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic Repeats	0	0	0.00	0.00	0	0	0.00	0.00
Total	0	0	0.00	0.00	0	0	0.00	0.00

Note: Total number of test (T) samples analyzed: 1428
Total number of reference (R) samples analyzed: 1470

Pivotal Fasting Bioequivalence Study No. 662/18 Valsartan								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used in reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic Repeats	0	0	0.00	0.00	0	0	0.00	0.00
Above Upper Limit of Quantification	07	09	0.47	0.58	07	09	0.47	0.58
Inconsistent Internal Standard Response	01	00	0.07	0.00	01	00	0.07	0.00
Total	08	09	0.54	0.58	08	09	0.54	0.58

Note: Total number of test (T) samples analyzed: 1496
Total number of reference (R) samples analyzed: 1540

Does the assessor 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 To be Determined
Did recalculation of PK parameters change the study outcome?	☐ Yes ☐ No ☐ N/A To be Determined
Are the PK parameters of reanalysis still within the acceptance limits for the 90% CI?	☐ Yes ☐ No ☐ N/A To be Determined

Comments on Bioanalytical Results: Incomplete

4.1.1.3.3.1 Assessor’s Comments on Reanalysis of Study Samples:

- During the pivotal fasting BE study, the applicant analyzed a total of 2898 sacubitril samples and 3036 valsartan samples. Of these samples, 17 valsartan samples (0.56%) were reanalyzed. The reassays were conducted based on SOP (b)(4) “Reanalysis of Study Samples”.

- Sixteen (16) valsartan samples were reassayed due to “Above Upper Limit of Quantification”. The assessor verified that these samples were correctly identified for reassay per SOP since their original concentrations were greater than the highest calibration standard (ULOQ, 10022 ng/mL). These samples were diluted 2-fold. Per SOP (b)(4) the samples were diluted using blank matrix. The pre-study method validation includes acceptable dilution integrity testing at 2-fold dilution of 20043 ng/mL. The repeat concentrations were within 15% of ULOQ after correcting for dilution factor except for repeat samples from Subjects (b)(6) whose repeat samples values were 24.2-66.2% lower than ULOQ. The applicant analyzed dilution quality control samples (DQCs) along with the repeat samples, and DQCs met the acceptance criteria per SOP. The available chromatograms for the original samples for Subjects (b)(6) and the chromatograms for the repeat samples do not indicate any processing or extraction errors. The applicant’s SOP states that [t]he dilution integrity is considered as qualified, if the %RE acceptance criteria ($\pm 15\%$ of the nominal concentration) for at least 50% of DQC sample(s). The repeated result is multiplied by the dilution factor and the resultant value is reported. However, the applicant will be asked to explain the significant difference between the aforementioned repeat samples and ULOQ and its impact on dilution integrity. The applicant repeated the analysis in singlet and reported the repeat value as the final concentration per SOP.
- One (1) valsartan sample was reassayed due to “Inconsistent Internal Standard Response”. The repeat sample is a pre-dose sample for Subject (b)(6) Period I. The assessor verified that this sample was correctly identified for reanalysis since the original internal standard (IS) response (IS peak area = 0) was outside 70% of the mean IS response of the accepted CCs, QCs, and Blank+IS in the respective run in accordance with SOP, which states:

“Inconsistent Internal Standard Response (IR)

Mean internal standard response is the mean response obtained from all the internal standard response of the accepted calibration curve standards, quality control samples and Blank+IS.

The unknown samples, whose internal standard response is beyond $\pm 70\%$ of the mean internal standard response, are repeated under the category of inconsistent internal standard response.

Samples under this category are analyzed in singlet and the results are reported...”

The applicant repeated the analysis in singlet and reported the repeat value as the final concentration per SOP.

4.1.1.3.3.2 Assessor’s Comments on Accepted and Rejected Runs:

- The applicant reported a total of 41 analytical runs for sacubitril and valsartan during the pivotal fasting BE study. No run was rejected.

4.1.1.3.3.3 Assessor's Comments on Re-injections:

- No re-injection was reported during the analysis of sacubitril and valsartan samples.

4.1.1.3.3.4 Assessor's Comments on Manual Re-Integration:

- No re-integration was reported during the analysis of sacubitril and valsartan samples.

4.1.1.3.3.5 Assessor's Comments on Incurred Sample Reanalysis (ISR):

Sacubitril

- The ISR was performed on 7.11% (206 samples) of the total number of sacubitril samples (2898 samples) per SOP (b)(4) which states that *10% of the samples should be reanalysed in case the number of samples is less than 1000 samples and 5% of the number of samples exceeding 1000 samples.*

The applicant's ISR sample selection is also consistent with the current Guidance for Industry, *Bioanalytical Method Validation* (May 2018), which states that *sample size required for ISR should be 10% reanalysis of the first 1000 samples, and 5% reanalysis of the remaining samples.* Per SOP and bioanalytical report, at least one sacubitril sample per period per subject was selected around C_{max} concentration and another with a concentration at least 3 times of LLOQ in the elimination phase.

- Per bioanalytical report, 94.17% of ISR samples (194 samples) were acceptable and within the acceptance criteria specified in the SOP:

“The assessment of ISR is considered acceptable if the percent difference of the original and reanalysis concentration are within $\pm 20.0\%$ of for chromatographic methods for at least 67% of the samples tested.”

Valsartan

- The ISR was performed on 6.78% (206 samples) of the total number of valsartan samples (3036 samples) per SOP (b)(4). The applicant's ISR sample selection is also consistent with the current Guidance for Industry, *Bioanalytical Method Validation* (May 2018) described above. Per SOP and bioanalytical report, at least one valsartan sample per period per subject was selected around C_{max} concentration and another with a concentration at least 3 times of LLOQ in the elimination phase.
- Per bioanalytical report, 85.44% of ISR samples (176 samples) were acceptable and within the acceptance criteria specified in the SOP.

The bioanalytical portion of the pivotal fasting BE study is **incomplete**.

4.1.1.4 Pharmacokinetic Results

4.1.1.4.1 Arithmetic Mean Pharmacokinetic Parameters – Assessor Calculated

Sacubitril

REPLICATE 1 (PERIODS 1 AND 2)

Parameter	Unit	Test				Reference				Ratio (T/R)
		Mean	CV%	Min	Max	Mean	CV%	Min	Max	
AUCT	ng.hr/mL	2952.723	24.70	1876.18	4859.07	2964.499	25.39	1617.21	4567.10	1.00
AUCINF	ng.hr/mL	3006.072	24.64	1889.03	4890.75	3007.952	24.88	1709.84	4601.49	1.00
C _{MAX}	ng/mL	2669.757	45.38	888.88	5335.80	2782.315	34.42	1012.60	5383.00	0.96
T _{MAX} *	hr	0.670	.	0.25	4.00	0.670	.	0.25	2.67	1.00
KEL	hr ⁻¹	1.023	28.55	0.43	1.76	1.006	32.49	0.43	1.83	1.02
THALF	hr	0.746	36.07	0.39	1.61	0.765	34.81	0.38	1.63	0.98

* T_{max} values are presented as median, range

REPLICATE 2 (PERIODS 3 AND 4)

Parameter	Unit	Test				Reference				Ratio (T/R)
		Mean	CV%	Min	Max	Mean	CV%	Min	Max	
AUCT	ng.hr/mL	2963.272	26.16	1727.37	4934.25	2933.641	26.88	1176.82	4441.59	1.01
AUCINF	ng.hr/mL	2995.648	25.89	1745.10	4972.14	3020.148	24.46	1708.49	4464.52	0.99
C _{MAX}	ng/mL	2864.658	39.48	761.17	4663.80	2656.247	48.42	869.16	6112.20	1.08
T _{MAX} *	hr	0.500	.	0.25	1.33	0.670	.	0.33	2.67	0.75
KEL	hr ⁻¹	1.097	25.91	0.55	1.82	1.096	25.43	0.58	1.70	1.00
THALF	hr	0.680	30.37	0.38	1.26	0.676	26.80	0.41	1.19	1.01

* T_{max} values are presented as median, range

ALL PERIODS (PERIODS 1, 2, 3, AND 4)

Parameter	Unit	Test				Reference				Ratio (T/R)
		Mean	CV%	Min	Max	Mean	CV%	Min	Max	
AUCT	ng.hr/mL	2957.842	25.23	1727.37	4934.25	2948.846	25.96	1176.82	4567.10	1.00
AUCINF	ng.hr/mL	3000.938	25.07	1745.10	4972.14	3014.050	24.49	1708.49	4601.49	1.00
C _{MAX}	ng/mL	2764.341	42.27	761.17	5335.80	2718.368	41.56	869.16	6112.20	1.02
T _{MAX} *	hr	0.670	.	0.25	4.00	0.670	.	0.25	2.67	1.00
KEL	hr ⁻¹	1.060	27.23	0.43	1.82	1.051	29.00	0.43	1.83	1.01
THALF	hr	0.714	33.75	0.38	1.61	0.720	31.99	0.38	1.63	0.99

* T_{max} values are presented as median, range

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Valsartan

REPLICATE 1 (PERIODS 1 AND 2)

Parameter	Unit	Test				Reference				Ratio (T/R)
		Mean	CV%	Min	Max	Mean	CV%	Min	Max	
AUCT	ng.hr/mL	34103.31	40.86	8593.66	64426.42	36406.73	39.77	8863.95	66711.11	0.94
AUCINF	ng.hr/mL	34396.08	40.56	8780.57	64824.12	36741.71	39.50	9011.04	67214.55	0.94
CMAX	ng/mL	5449.869	39.13	1346.60	9768.50	5977.991	37.13	1052.10	9961.20	0.91
TMAX*	hr	2.000	.	1.00	4.50	1.670	.	1.00	3.50	1.20
KEL	hr-1	0.107	24.70	0.06	0.19	0.107	23.78	0.06	0.17	1.00
THALF	hr	6.845	24.69	3.72	12.11	6.850	26.60	4.09	12.48	1.00

* T_{max} values are presented as median, range

REPLICATE 2 (PERIODS 3 AND 4)

Parameter	Unit	Test				Reference				Ratio (T/R)
		Mean	CV%	Min	Max	Mean	CV%	Min	Max	
AUCT	ng.hr/mL	37661.94	41.25	3628.61	71740.83	39895.43	34.61	8023.72	67563.12	0.94
AUCINF	ng.hr/mL	38003.77	40.89	3941.26	72188.25	40230.01	34.43	8263.17	68279.29	0.94
CMAX	ng/mL	6046.547	42.57	631.26	11733.00	6432.734	34.65	1234.90	11220.00	0.94
TMAX*	hr	2.000	.	1.33	4.50	2.330	.	1.33	4.00	0.86
KEL	hr-1	0.104	24.24	0.07	0.18	0.108	22.04	0.07	0.16	0.97
THALF	hr	6.977	21.04	3.91	10.22	6.728	21.49	4.28	9.50	1.04

* T_{max} values are presented as median, range

ALL PERIODS (PERIODS 1, 2, 3, AND 4)

Parameter	Unit	Test				Reference				Ratio (T/R)
		Mean	CV%	Min	Max	Mean	CV%	Min	Max	
AUCT	ng.hr/mL	35830.29	41.12	3628.61	71740.83	38176.36	37.06	8023.72	67563.12	0.94
AUCINF	ng.hr/mL	36146.87	40.79	3941.26	72188.25	38511.14	36.84	8263.17	68279.29	0.94
CMAX	ng/mL	5739.433	41.09	631.26	11733.00	6208.658	35.75	1052.10	11220.00	0.92
TMAX*	hr	2.000	.	1.00	4.50	2.000	.	1.00	4.00	1.00
KEL	hr-1	0.106	24.34	0.06	0.19	0.108	22.74	0.06	0.17	0.98
THALF	hr	6.909	22.81	3.72	12.11	6.788	24.03	4.09	12.48	1.02

* T_{max} values are presented as median, range

4.1.1.4.2 Geometric Means and 90% Confidence Intervals - Applicant Calculated

Sacubitril and Valsartan Tablets 97 mg/103 mg (No of subjects completed= 35) Dose (1 × 97 mg/103 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals

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Fasting Bioequivalence Study (Study No. 662/18) (Sacubitril)						
Parameter	Test	N	Reference	N	Ratio (%)	90% C.I.
AUC _t (hr*ng /mL)	2842.848	68	2822.448	69	100.19	97.89-103.64
AUC _{inf} (hr*ng /mL)	2884.404	67	2894.228	68	100.21	97.10-102.29
C _{max} (ng/ml)	2477.042	68	2486.004	69	98.00	90.51-109.69

Fasting Bioequivalence Study (Study No. 662/18) (Valsartan)						
Parameter	Test	N	Reference	N	Ratio (%)	90% C.I.
AUC _t (hr*ng /mL)	31909.11	68	35068.26	69	90.72	81.43-101.68
AUC _{inf} (hr*ng /mL)	32276.93	68	35419.47	69	90.86	81.68-101.66
C _{max} (ng/ml)	5125.141	68	5727.119	69	89.37	78.93-101.46

For AUC_t & AUC_{inf}, the S_{WR} is < 0.294, hence conventional average bioequivalence approach was used for the calculation and the results are represented in bold.

Fasting Bioequivalence Study (Study No. 662/18) (Sacubitril)								
Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	95% Criteria Bound	Method Used	Outcome
LAUCT	100.19	97.89	103.64	0.009	0.09329	-0.004816	MIXED	PASS
LAUCI	100.21	97.10	102.29	0.008	0.08994	-0.004459	MIXED	PASS
LCMAX	98.00	90.51	109.69	0.120	0.34636	-0.065356	MIXED	PASS

Fasting Bioequivalence Study (Study No. 662/18) (Valsartan)								
Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	Outcome
LAUCT	90.72	81.43	101.68	0.067	0.25853	-0.005983	MIXED	PASS
LAUCI	90.86	81.68	101.66	0.065	0.25480	-0.005902	MIXED	PASS
LCMAX	89.37	78.93	101.46	0.092	0.30393	-0.010139	MIXED	PASS

For AUC_t & AUC_{inf}, the S_{WR} is < 0.294, hence, conventional average bioequivalence approach was used for the calculation and the results are represented in bold.

For C_{max}, the S_{WR} is > 0.294, hence, reference-scaled average bioequivalence approach was used for the calculation and the results are represented in bold.

4.1.1.4.3 Geometric Means and 90% Confidence Intervals - Assessor Calculated

Sacubitril and Valsartan Tablet 1 × 97 mg/103 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fasting Bioequivalence Study No. 662/18 Sacubitril Unscaled Data						
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.

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AUC_{0-t} (hr.ng/ml)	2842.85	68	2822.45	69	1.01	97.89	103.64
AUC_∞ (hr.ng/ml)	2884.40	68	2894.23	69	1.00	97.10	102.29
C_{max} (ng/ml)	2477.04	68	2486.00	69	1.00	90.51	109.69

Scaled Data								
Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	S ² _{WR}	SWR	Criteria Bound	Method Used	Outcome
LnAUC _{0-t}	1.00	97.89	103.64	0.0087022	0.0932858	-0.004816	Unscaled	PASS
LnAUC _{0-inf}	1.00	97.10	102.29	0.0080885	0.089936	-0.004459	Unscaled	PASS
LnC _{max}	0.98	90.51	109.69	0.1199647	0.3463593	-0.065356	Scaled/PE	PASS

Sacubitril and Valsartan Tablet 1 × 97 mg/103 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasting Bioequivalence Study No. 662/18							
Valsartan							
Unscaled Data							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
AUC _{0-t} (hr.ng/ml)	31909.11	68	35068.25	69	0.91	81.43	101.68
AUC _∞ (hr.ng/ml)	32276.93	68	35419.47	69	0.91	81.68	101.66
C _{max} (ng/ml)	5125.14	68	5727.12	69	0.89	78.93	101.46

Scaled Data								
Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	S ² _{WR}	SWR	Criteria Bound	Method Used	Outcome
LnAUC _{0-t}	0.91	81.43	101.68	0.0668375	0.2585296	-0.005983	Unscaled	PASS
LnAUC _{0-inf}	0.91	81.68	101.66	0.0649223	0.2547985	-0.005902	Unscaled	PASS
LnC _{max}	0.89	78.93	101.46	0.0923752	0.3039329	-0.010139	Scaled/PE	PASS

4.1.1.4.4 Additional Information for the Study

SWR*	Sacubitril
	AUC _i : 0.0932
	AUC _i : 0.0899
	C _{max} : 0.3463
	Valsartan
	AUC _i : 0.2585
AUC _i : 0.2548	
C _{max} : 0.3040	

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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).	Sacubitril ☐ Yes ☒ No Valsartan ☐ Yes ☒ No
Were the subjects dosed in groups? If yes, was the statistical analysis proper? Is reanalysis by assessor necessary?	Sacubitril ☐ Yes ☒ No Valsartan ☐ Yes ☒ No
Are there measurable drug concentrations at 0 hr? If yes, please comment (and take necessary action, if needed).	Sacubitril ☐ Yes ☒ No Valsartan ☐ Yes ☒ No
Are there first measurable drug concentration as C_{max}? If yes, please comment.	Sacubitril ☐ Yes ☒ No Valsartan ☐ Yes ☒ No
Are there C_{max} at the first time point? If yes, is the study (sample) design adequate?	Sacubitril ☐ Yes ☒ No Valsartan ☐ Yes ☒ No

* The assessor used SAS code “Highly Variable 4-way Crossover “HV-RefScale4Period-ver1.SAS” for statistical analysis. This SAS code does not generate results for Root Mean Square Error (RMSE). Therefore, the assessor included S_{WR} values in place of RMSE.

Ratio of $AUC_{0-t}/AUC_{0-\infty}$ *				
Treatment	n	Mean	Minimum	Maximum
Sacubitril				
Test	68	0.99	0.95	0.99
Reference	69	0.99	0.93	1.00
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below.	N/A			
Valsartan				
Test	68	0.99	0.92	1.00
Reference	69	0.99	0.97	1.00
If the minimum ratios less than 0.8, were they due to inadequate sampling	N/A			

schedule? Provide additional comments below.	

* Calculated by the assessor (SAS code HV-RefScale4Period-ver1.SAS does not provide AUC ratio in its output). AUC ratio calculations are provided in Column #11 of PK sheet within the spreadsheet dataset in [Section. 4.4.3.](#)

Comments on Pharmacokinetic Results: Adequate

- This is an immediate-release (IR) product. The median T_{max} (range) values reported for sacubitril and valsartan during the pivotal fasting BE study were as follows:

Analyte	T _{max} Test (hours)	T _{max} Reference (hours)	Ratio
Sacubitril	0.67 (0.25-4.00)	0.67 (0.25-2.67)	1.00
Valsartan	2.00 (1.00-4.50)	2.00 (1.00-4.00)	1.00

Based on the T/R ratios calculated above for sacubitril and valsartan, the assessor considers the T_{max} for the test and reference product in the pivotal fasting BE study comparable.

- The applicant proposed to use either the unscaled average BE procedure or the reference-scaled average BE procedure for analyzing sacubitril and valsartan BE parameters in its study protocol depending on the intra-subject variability (S_{WR}) as described below:

“If the S_{WR} < 0.294 Two one-sided test procedure is used to determine bioequivalence (BE) for the specific primary pharmacokinetic (PK) parameters C_{max}, AUC_t and AUC_{inf}.”

- *The 90% two one sided confidence intervals for the primary PK parameters are within the 80.00% to 125.00% for Sacubitril and Valsartan.*

If the S_{WR} ≥ 0.294 the reference scaled procedure is used to determine BE for the specific primary pharmacokinetic parameters C_{max}, AUC_t and AUC_{inf}.”

Test product is considered as bioequivalent with the reference product if the both of the following conditions are met for each primary PK parameter tested:

- *The 95% upper confidence bound for $(\mu_T - \mu_R)^2 - \theta \cdot S^2_{WR}$ must be ≤ 0 .
Where $\theta = (\ln(1.25)/0.25)^2$*
- *The point estimate of the Test/Reference geometric mean ratio must fall within [0.80, 1.25] for Sacubitril and Valsartan.”*

Since the S_{WR} for sacubitril and valsartan was < 0.294 for AUC_t and AUC_i and > 0.294 for C_{max} the applicant used the unscaled average BE procedure for AUC_t and AUC_i and reference-scaled procedure for C_{max}. According to the clinical study

protocol, all evaluable subjects completing all at least two periods of the study were included in the statistical analysis.

- The assessor used Highly Variable 4-way Crossover SAS program with SAS code CONTINU to analyze the data (HV-RefScale4Period-ver1.SAS). The SAS program contained the standard BE approach (unscaled data) and reference scaled BE approach (scaled data). Both scaled and unscaled approaches use SAS PROC MIXED procedure. The applicant used SAS PROC MIXED procedure for the evaluation of within-subject variability, which is the same as the assessor's.
- Since the S_{WR} was < 0.294 for AUC_t and AUC_i for sacubitril and valsartan, the unscaled average BE procedure was used to evaluate the least squares geometric means of AUC_t and AUC_i while reference-scaled procedure was used for C_{max} since S_{WR} was > 0.294 . The results of the unscaled data showed that the 90% C.I. values for the least squares geometric means of AUC_t and AUC_i of sacubitril and valsartan in the pivotal fasting BE study were within the acceptable BE limits of 80.00-125.00%.
- The 95% upper confidence bounds for $(\mu_T - \mu_R)^2 - \theta S^2_{WR}$ for C_{max} of sacubitril and valsartan in the pivotal fasting BE study were < 0 , meeting the first condition²⁴. The point estimates (T/R mean ratio) for C_{max} of sacubitril and valsartan in the pivotal fasting BE study were within [0.8, 1.25], meeting the second condition.
- The assessor's analysis for both sacubitril and valsartan are similar to the applicant's results and thus confirmed the applicant's conclusion.

The pharmacokinetic portion of the pivotal fasting BE study is **adequate**.

4.1.1.5 Overall Comment

Was the pivotal fasting bioequivalence study acceptable? No, due to bioanalytical and method validation deficiencies.

²⁴ S. H. Haidar, B. Davit, M. L. Chen, et al., Bioequivalence Approaches for Highly Variable Drugs and Drug Products. *Pharm. Res.* **25**:237-41 (2008) and Davit et al., Implementation of a Reference-Scaled Bioequivalence Approach for Highly Variable Generic Drug Products by the US Food and Drug Administration. *The AAPS Journal*, 2012.

Mean Plasma Concentrations, Single-Dose Pivotal Fasting Bioequivalence Study - Assessor Calculated

Sacubitril					
Time (hr)	Test (n = 68)		Reference (n = 69)		T/R Ratio
	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	
0	0.00	.	0.00	.	-
0.08	48.95	257.77	34.51	325.31	1.42
0.17	511.21	144.68	398.73	155.21	1.28
0.25	1102.54	105.46	1035.90	93.21	1.06
0.33	1654.43	70.65	1655.00	72.75	1.00
0.5	2294.60	50.91	2248.64	45.89	1.02
0.67	2234.30	48.65	2213.72	47.30	1.01
0.83	1791.08	51.26	1827.84	47.38	0.98
1	1350.01	57.17	1416.44	50.00	0.95
1.33	812.31	53.84	820.54	53.29	0.99
1.67	549.98	57.39	563.98	63.96	0.98
2	449.21	78.78	451.55	79.48	0.99
2.33	362.60	69.26	346.03	89.41	1.05
2.67	305.93	101.30	343.70	112.55	0.89
3	266.32	110.16	296.10	100.20	0.90
4	164.03	140.72	138.01	132.47	1.19
5	56.24	146.58	45.31	156.46	1.24
6	14.02	177.22	10.88	201.15	1.29
8	0.33	824.62	0.88	594.13	0.38
10	0.00	.	0.00	.	-
12	0.00	.	0.00	.	-

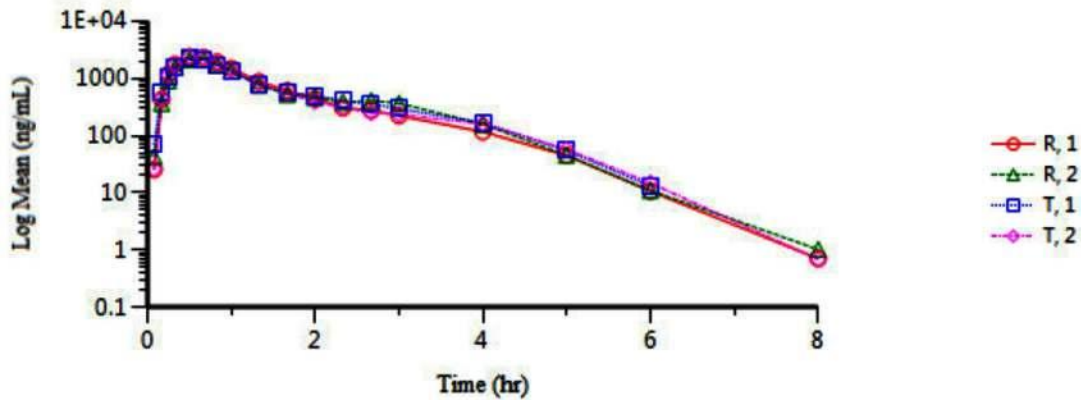
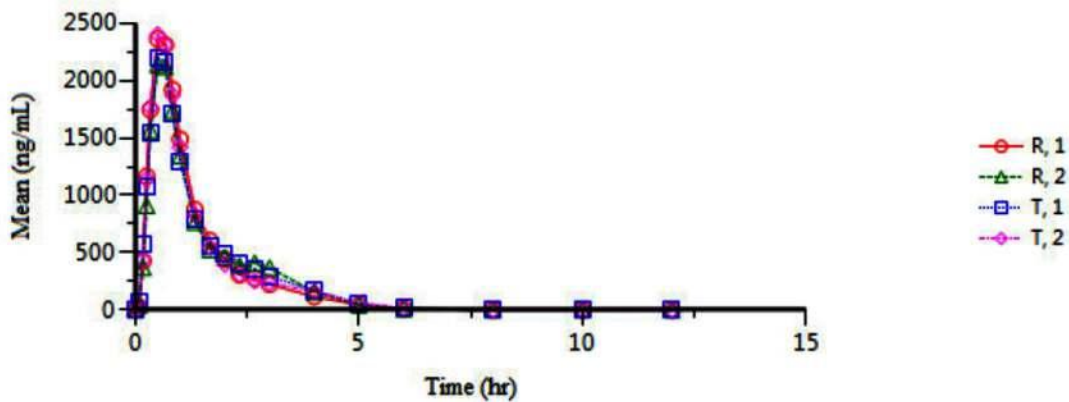
Valsartan					
Time (hr)	Test (n = 68)		Reference (n = 69)		T/R Ratio
	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	
0	0	.	0	.	-
0.33	682.32	46.02	752.83	44.87	0.91
0.67	2161.31	44.46	2394.11	42.97	0.90
1	3711	44.59	4138.81	40.76	0.90
1.33	4736.61	43.33	5276.29	38.74	0.90
1.67	5141.9	44.34	5679.4	40.23	0.91
2	5102.77	44.65	5685.37	40.29	0.90
2.33	5100.54	44.64	5376.91	41.18	0.95
2.67	4950.91	45.74	5203.54	39.07	0.95
3	4702.9	44.75	5027.4	40.64	0.94
3.5	4407.79	43.68	4636.39	40.27	0.95
4	4024.64	43.49	4287.44	39.52	0.94

ANDA 213676
Single-Dose Pivotal Fasting Bioequivalence Study Assessment

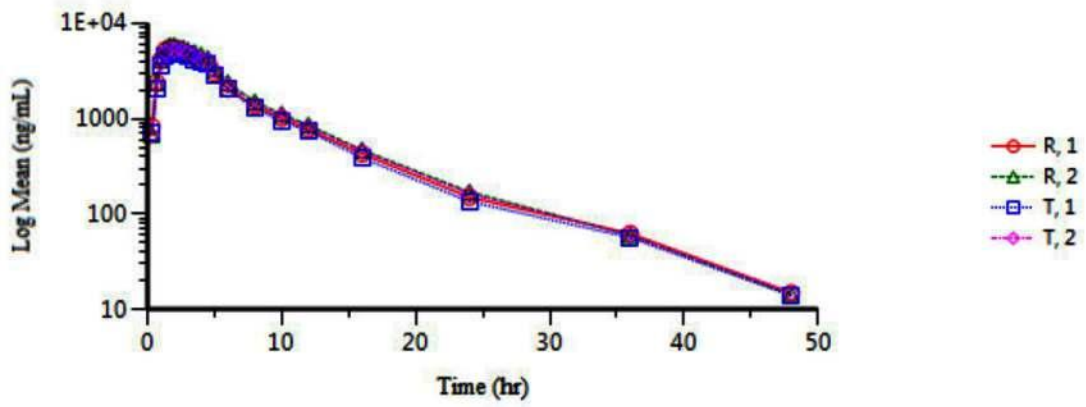
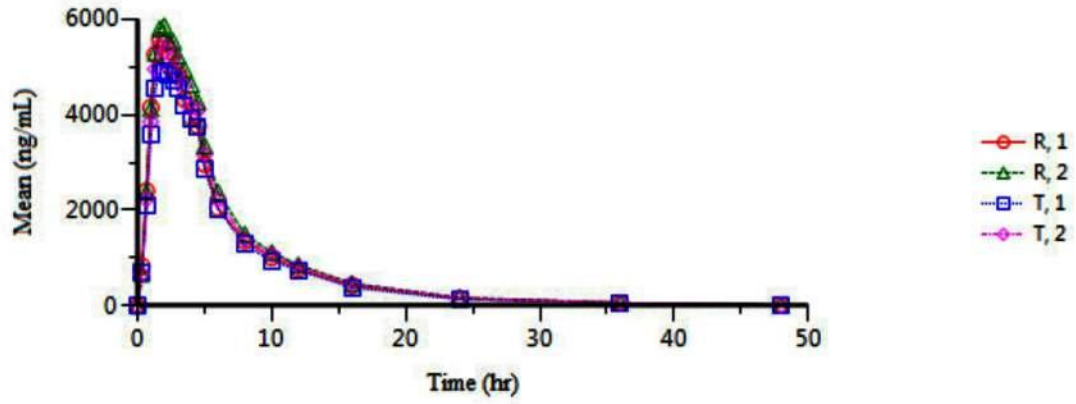
Valsartan					
Time (hr)	Test (n = 68)		Reference (n = 69)		T/R Ratio
	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	
4.5	3911.4	44.49	4016.42	40.31	0.97
5	3015.89	42.35	3157.56	41.14	0.96
6	2130.75	42.4	2213.32	38.11	0.96
8	1329.26	43.35	1424.94	37.31	0.93
10	1010.86	43.77	1065.19	39.25	0.95
12	775.96	44.38	812.43	38.46	0.96
16	421.09	47.92	448.66	43.88	0.94
24	149.04	53.39	160.85	51.27	0.93
36	58.54	55.07	61.34	56.24	0.95
48	14.43	106.16	14.67	114.54	0.98

Mean Plasma Concentrations, Single-Dose Pivotal Fasting Bioequivalence Study – Assessor Calculated

Sacubitril



Valsartan



4.1.2 Single-Dose Pivotal Fed Bioequivalence Study

4.1.2.1 Study Design

4.1.2.1.1 Study Information

Study Number	663/18	
Study Title	An open label, balanced, randomized, two-treatment, four-period, two-sequence, single dose, crossover, full-replicate, oral bioequivalence study of Sacubitril and Valsartan tablets 97 mg/103 mg of Laurus Labs Limited, India comparing with ENTRESTO™ (sacubitril / valsartan) tablets 97 mg/103 mg of Novartis Pharmaceuticals Corp East Hanover, NJ 07936 in healthy, adult, human subjects under fed conditions	
Clinical Site (Name & Address)	QPS Bioserve India Pvt. Limited, # 6-56/6/1A, Opp: IDPL Factory, Balanagar, Hyderabad-500 037, Telangana, India. Tel: +91-40-4377 0873 / 1875 Fax: +91-40-4377 0877	
Principal Clinical Investigator	Dr. K.Babji babji.kalmanoor @qpsbioserve.com	
Dosing Dates	Period I: 21/02/2019 Period II: 01/03/2019 Period III: 09/03/2019 Period IV: 17/03/2019	
Analytical Site (Name & Address)	(b)(4)	
Analysis Dates	20/03/2019 - 11/04/2019	
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)	(21/02/2019 to 11/04/2019) 50 days	
(b) Temperature Range (e.g., -20°C to -80°C)	-20°C ± 10°C	
Long-Term Storage Stability (LTSS) Coverage (no. days @ temp °C)	154 days @ -20°C ± 10°C and -70° ± 15°C	

4.1.2.1.2 Product (Bio-batch) Information

- Same as the pivotal fasting BE study

4.1.2.1.3 Study Design, Single-Dose Pivotal Fed Bioequivalence Study

Number of Subjects	Enrolled: 28 Dosed: 28 Completed: 28 completed at least 2 periods and 26 completed all periods Samples Analyzed: 28 Statistically Analyzed: 28
No. of Sequences	2
No. of Periods	4
No. of Treatments	2
No. of Groups	1
Washout Period	8 days
Randomization	☒ Yes ☐ No
Blood Sampling Times	Blood samples were collected at pre-dose (0 hour) and 0.17, 0.33, 0.50, 0.67, 0.83, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00, 3.33, 3.67, 4.00, 4.50, 5.00, 5.50, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00, 36.00 and 48.00 hours post dose.
IRB Approval	☒ Yes Date: 24/12/2018 ☐ No
Informed Consent	☒ Yes Date: 24/12/2018 ☐ No
Length of Fasting	An overnight fast of at least 10 hours prior to the start of a high fat, high calorie breakfast and at least 4 hours post-dose except for the high-fat high-caloric breakfast meal taken 30 minute before dosing.
Length of Confinement	At least 11 hours prior to dosing until 48.00 hours post-dose blood sample collection.
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			
If No, then meal components and composition are listed in the table below.					
Composition of Non-standard FDA Meal Used in the Pivotal Fed Bioequivalence Study					
Ingredients	Amount (g)	Protein (g)	Fat (g)	Carbohydrate (g)	Energy (Cal)
Bread toast with butter	34 g of bread with 20 g of butter	2.81	16.45	18.68	234.01
Egg omelet	27	3.99	8.99	----	96.87
Fried chicken	72	19.43	10.45	----	171.77
Potato cutlet	110	2.40	15.15	33.90	281.55
Milk	240 ml	8.64	8.10	12.42	157.14

Total (g)	37.27	59.14	65.00	—
Total (Cal)	149.08	532.26	260.00	941.34
Percentage (%)	15.84	56.54	27.62	100

Comments on Study Design: Adequate

- The study design for the pivotal fed BE study (Study No. 663/18) was an open label, single-dose, randomized, two-treatment, four-period, two-sequence, full-replicate, crossover BE study, which is not in line with the recommendation in the PSG for Sacubitril and Valsartan Tablets, 97 mg/103 mg. The applicant did not provide an explanation for its selected BE study design. It is noted that the applicant conducted pilot fed BE study (Study No. 059/18) as recommended in the PSG (i.e. single-dose, two-way crossover study), which failed to meet the BE acceptance limits possibly due to high intra-subject variability observed during the pilot BE study under fed condition. As with the pivotal fasting BE study, the assessor deems the applicant's BE study design acceptable for the following reasons:
 - 1) The applicant's pilot fed BE study conducted per PSG recommendation failed to meet the BE limit for C_{max} for sacubitril and valsartan presumably due to highly intra-subject variability.
 - 2) The applicant has pre-established the fully-replicate study design prior to conducting the pivotal fed BE study.
 - 3) In ORS's responses to Controlled Correspondence no. 23610606²² and no. 24442067²³ for the same drug product, ORS concluded that a fully replicated crossover BE study design under fed conditions is acceptable for the current drug product provided that the applicant provides evidence of high variability (i.e. $swr \geq 0.294$) in the pharmacokinetic parameters (C_{max} and/or AUC) of the reference product. In the current pivotal fed BE study, swr value for C_{max} for sacubitril was ≥ 0.294 . Therefore, for sacubitril, the applicant used the reference-scaled average approach to demonstrate BE for C_{max} and the conventional two one-sided test procedure to demonstrate BE for AUC_{0-t} and $AUC_{0-\infty}$. For valsartan, the applicant used the conventional two one-sided test procedure to demonstrate BE for all pharmacokinetic parameters.
- Per RLD labeling⁶, following oral administration, the peak plasma concentrations for sacubitril and valsartan occurred between 0.5 and 1.5 hours, respectively. In addition, sacubitril and valsartan have terminal elimination half-lives of approximately 1.4 and 9.9 hours, respectively. Food intake resulted in decreased exposure to valsartan, but this decrease is not clinically significant. Food intake has no clinically significant effect on the systemic exposures of sacubitril or LBQ657. The applicant collected blood samples up to 48 hours post-dose, which is adequate to capture the T_{max} and elimination phase with no first time point C_{max} observed. The washout period of 8 days between study periods is more than five half-lives of sacubitril and valsartan and thus is sufficient to ensure the complete elimination of remaining sacubitril and valsartan before the next dosing period.

- As with the pivotal fasting BE study, the current PSG on Sacubitril and Valsartan Tablets, 97 mg/103 mg recommends that fed BE study be conducted in *[h]ealthy males and females (nonpregnant), general population. Female subjects should not be pregnant or lactating, and if applicable, should practice abstinence or contraception during the study.* Per clinical study report, the pivotal fed BE study was conducted in male subjects only and thus in line with the recommendations in the current PSG.

The pivotal fed BE study design is **adequate**.

4.1.2.2 Clinical Results

4.1.2.2.1 Demographic Profile of Subjects

Pivotal Fed Bioequivalence Study No. 663/18			
		Treatment Groups	
		Test Product N = 28	Reference Product N = 28
Age (years)	Mean ± SD	31.2 ± 5.3	31.2 ± 5.3
	Range	22.0 - 44.0	22.0 - 44.0
Age Groups	< 18	0 (0.00%)	0 (0.00%)
	18 – 40	27 (96.43%)	27 (96.43%)
	41 – 64	01 (3.57%)	01 (3.57%)
	65 – 75	0 (0.00%)	0 (0.00%)
	> 75	0 (0.00%)	0 (0.00%)
Sex	Male	28 (100.0%)	28 (100.0%)
	Female	0 (0.00%)	0 (0.00%)
Race	Asian	28 (100.0%)	28 (100.0%)
	Black	0 (0.00%)	0 (0.00%)
	Caucasian	0 (0.00%)	0 (0.00%)
	Hispanic	0 (0.00%)	0 (0.00%)
	Other	0 (0.00%)	0 (0.00%)
BMI	Mean ± SD	23.1 ± 1.9	23.1 ± 1.9
	Range	18.6 - 24.8	18.6 - 24.8
Other Factors		NA	NA

NA=Not Applicable

Is the demographics profile of subjects completing the bioequivalence study in agreement with the current drug product recommendation? If no, please comment.	☒ Yes ☐ No

4.1.2.2.2 Dropout Information

Subject No.	Reason	Period	Replaced?
(b)(6)	Subject was withdrawn from period-II due to adverse event (vomiting) after dosing in period-II.	II	No
	Subject did not turn up for period-III check-in.	III	No

Are dropouts appropriate? If no, please comment.	☒ Yes ☐ No ☐ N/A

4.1.2.2.3 Study Adverse Events

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Pivotal Fed Bioequivalence Study No. 663/18	
	Test (N = 28)	Reference (N = 28)
Gastrointestinal disorders		
Diarrhea	01 (3.57%)	-
Vomiting	01 (3.57%)	-
Respiratory, thoracic and mediastinal disorders		
Dry cough	01 (3.57%)	-
Cough	01 (3.57%)	-
Skin and subcutaneous tissue disorders		
Itching all over body	03 (10.71%)	01 (3.57%)
Musculoskeletal and connective tissue disorders		
Body pains	01 (3.57%)	-
Total	08 (28.57%)	01(3.57%)

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 T _{max} 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 ☐ N/A (See comments below)
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/CSSS via the OGD-PremarketSafetyReports@fda.hhs.gov mailbox?	☐ 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

Type	Subject #s (Test T)	Subject #s (Reference R)
In House Blood Draw deviation	Period-II	
	-	S16 (2.33hr)

If the applicant 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

- A total of 28 subjects were enrolled and dosed in the pivotal fed BE study. Per clinical study report, Subject [redacted] discontinued from period II post-dose due to adverse event of vomiting. Subject [redacted] did not turn up to the clinical facility for period III check-in. The assessor checked the study protocol and CRFs for the above subjects and verified that Subject [redacted] returned for period III-IV following discontinuation from period II and Subject [redacted] returned for period IV following discontinuation from period III, which was in line with the study protocol. The collected samples were analyzed and considered for pharmacokinetic and statistical analyses with the remaining subjects since they completed at least 2 study periods, which is in line with the study protocol.
- Per the clinical study report, 9 AEs were reported following administration of the test and reference products in all study periods I-IV. Most of these AEs are listed in the RLD labeling. Per the clinical study report and CRFs, the reported AEs was considered to be moderate and possibly or unlikely related to the study treatment. These AEs were resolved by the end of study without any sequelae. Based on the number of observed AEs, the AE profile are not comparable between test and reference treatments. However, since the majority of AEs are single incidence and the subjects who had these AEs did not have any other complaints upon check-out, the assessor does not consider the above reported AE would impact the BE study outcome.
- According to the clinical study report, Subjects [redacted] (b)(6) received the following concomitant medications orally: TusQ-X + (Terbutaline Sulphate, Ambroxol Hydrochloride and Guaifenesin) Syrup, Paracetamol Tablets, Lactic Acid Bacillus Tablets, and Norflox TZ (Norfloxacin, Tinidazole, Lactic Acid Bacillus Tablets). In addition, Subjects [redacted] (b)(6) received the following concomitant medication intravenously: Pheniramine Maleate Injection and Ondansetron Injection. The applicant’s pre-study method validation includes the evaluation of aforementioned concomitant medications except Lactic Acid Bacillus, which was administered to Subject [redacted] who suffered from diarrhea.

However, Subject [redacted] received Lactic Acid Bacillus at 5 hours and 37 minutes and at 9 hours and 54 minutes after drug administration, and Subject (b)(6) C_{max} for valsartan and sacubitril was observed at 2.33 and 1.00 hours, respectively. Therefore, since Lactic Acid Bacillus was administered in the elimination phase of Subject [redacted] this concomitant medication should not significantly affect the BE study outcome. Per the pre-study method validation report, the applicant demonstrated that the aforementioned concomitant medications do not interfere with the analytical measurement of valsartan and sacubitril. Therefore, the assessor does not consider these concomitant medications will impact the study outcome.

- The applicant reported one protocol deviation of In House Blood Draw deviation for Subject (b)(6) as the sampling collection time at 2.33 hour time point deviated by 4 minutes due to cannula blockage. According to the clinical study report, the applicant used actual blood sampling time points for the calculation of pharmacokinetic parameters. The assessor also used actual blood sampling time points. Therefore, the assessor does not consider this protocol deviation would affect the calculation of pharmacokinetic parameters and the study outcome.

The handling of adverse events, dropouts, and protocol deviations is **acceptable**.

4.1.2.3 Bioanalytical Results

4.1.2.3.1 SOPs dealing with Sample Analysis including Repeat Analysis

Same as the pivotal fasting BE study.

4.1.2.3.2 Sample Analysis Calibration and Quality Control

Pivotal Fed Bioequivalence Study No. 663/18 Sacubitril										
Parameter	Standard Curve Samples									
Concentration (ng/mL)	20.124	40.249	100.62	240.15	600.37	1563.5	3602.5	7204.9	10802	12002
Inter day Precision (%CV)	1.1	2.1	1.5	2.6	2.8	1.8	2.6	1.7	3.5	2.3
Inter day Accuracy (%Actual)	99.5	100.1	101.3	101.9	101.4	101.6	99.9	98.8	97.1	98.4
Linearity (R ²)	0.9964 to 0.9998									
Linearity Range (ng/mL)	20.124 to 12002									
Sensitivity/LOQ (ng/mL)	20.124									

Parameter	Quality Control Samples				
	HQC	MQC	AQC-I	AQC-II	LQC
Concentration (ng/mL)	9120.3	4204.4	1324.4	483.41	58.009
Inter day Precision (%CV)	2.2	2.1	2.5	2.0	3.0
Inter day Accuracy (%Actual)	97.9	100.4	102.9	103.4	103.3

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Pivotal Fed Bioequivalence Study No. 663/18										
Valsartan										
Parameter	Standard Curve Samples									
Concentration (ng/mL)	16.804	33.607	84.019	200.52	501.31	1305.5	3008.0	6016.0	9019.6	10022
Inter day Precision (%CV)	1.2	2.7	3.1	2.5	2.6	1.9	3.7	1.6	3.0	1.8
Inter day Accuracy (%Actual)	99.3	100.4	101.2	101.7	102.0	101.2	100.4	98.7	97.7	97.4
Linearity (R ²)	0.9956 to 0.9998									
Linearity Range (ng/mL)	16.804 to 10022									
Sensitivity/LOQ (ng/mL)	16.804									

Parameter	Quality Control Samples				
	HQC	MQC	AQC-I	AQC-II	LQC
Concentration (ng/mL)	7615.3	3510.7	1105.9	403.64	48.437
Inter day Precision (%CV)	2.3	2.2	2.6	2.4	3.2
Inter day Accuracy (%Actual)	98.4	100.4	102.6	103.3	103.2

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	☒ Yes ☐ No
Are there any concerns related to sample analysis (including rejected runs, reinjection, sample dilution, etc.)? If yes, comment below or consult TL/tertiary assessor for additional actions	☐ Yes ☒ No
Were 20% of chromatograms included?	☒ Yes ☐ No
Were chromatograms serially or randomly selected?	☒ serially ☐ randomly (Subjects (b)(6))
Any interfering peaks in chromatograms?	☐ Yes ☒ No
Were the chromatograms submitted by the applicant acceptable?	☒ Yes ☐ No
Were 100% raw analytical data, including failed runs, provided?	☒ Yes ☐ No

4.1.2.3.3 Reanalysis of Study Samples

Pivotal Fed Bioequivalence Study No. 663/18								
Sacubitril								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used in reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic Repeats	00	00	0.00	0.00	00	00	0.00	0.00
Incomplete Analysis	02	00	0.16	0.00	02	00	0.16	0.00
Total	02	00	0.16	0.00	02	00	0.16	0.00

Note: Total number of test (T) samples analyzed: 1270

Total number of reference (R) samples analyzed: 1265

Pivotal Fed Bioequivalence Study No. 663/18								
Valsartan								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used in reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic Repeats	00	00	0.00	0.00	00	00	0.00	0.00
Incomplete Analysis	02	00	0.13	0.00	02	00	0.13	0.00
Total	02	00	0.13	0.00	02	00	0.13	0.00

Note: Total number of test (T) samples analyzed: 1496
Total number of reference (R) samples analyzed: 1540

Does the assessor agree with the reanalysis of study samples: analytical and/or PK repeat?	☒ Yes ☐ No ☐ N/A
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.

4.1.2.3.3.1 Assessor’s Comments on Reanalysis of Study Samples:

- During the pivotal fed BE study, the applicant analyzed a total of 2535 sacubitril samples and 2643 valsartan samples. Of these samples, 2 sacubitril samples and 2 valsartan samples (0.08%) were reanalyzed. The reassays were conducted based on SOP (b)(4) ‘Reanalysis of Study Samples’.
- Two (2) sacubitril samples and 2 valsartan samples were reassayed due to ‘Incomplete Analysis’. The repeat samples are for Subject (b)(4) Period I, 1.33 hours and Subject (b)(4) Period I, 1.00 hour. The assessor verified that these samples were correctly identified for reanalysis since no analyte or internal standard responses were measured for the original samples as indicated by the numerical raw data and the bioanalytical report. SOP (b)(4) states:

“Incomplete Analysis (IA)

Any sample for which a chromatogram cannot be obtained due to technical reasons (such as sample lost during processing, processing error, sample loading error in auto sampler tray, injection carryover, auto sampler vial breakage during instrument analysis, instrument malfunction, retention time shifting etc.) is reanalysed under the category of incomplete analysis.

If any sample shows no peak at the internal standard retention time (except for blank samples), then that sample is repeated under the category of incomplete analysis.

Samples under this category are analyzed in singlet and the results are reported...

Per bioanalytical report, the reasons for reassaying these samples were due to sample loss during processing and during flash freezing. The applicant repeated the analysis in singlet and reported the repeat values as the final concentrations per SOP.

4.1.2.3.3.2 Assessor's Comments on Accepted and Rejected Runs:

- The applicant reported a total of 33 analytical runs for sacubitril and valsartan during the pivotal fasting BE study. No run was rejected.

4.1.2.3.3.3 Assessor's Comments on Re-injections:

- No re-injection was reported during the analysis of sacubitril and valsartan samples.

4.1.2.3.3.4 Assessor's Comments on Manual Re-Integration:

- The applicant reported one (1) sample was re-integrated during the analysis of sacubitril samples due to "Expected RT updated for proper Peak Integration". The re-integrated sample is a QC sample (HQC-358). The assessor checked the original chromatogram for the re-integrated sample and verified that the analyte peak was not properly captured for integration. Since this is a QC sample and the exclusion of this QC will not impact run acceptability, the assessor does not consider this re-integration would impact the study outcome.

4.1.2.3.3.5 Assessor's Comments on Incurred Sample Reanalysis (ISR):

Sacubitril

- The ISR was performed on 7.57% (192 samples) of the total number of sacubitril samples (2535 samples) per SOP (b)(4). The applicant's ISR sample selection is also consistent with the current Guidance for Industry, *Bioanalytical Method Validation* (May 2018) described in [Section 4.1.1.3.3.5](#). Per SOP and bioanalytical report, at least one sacubitril sample per period per subject was selected around C_{max} concentration and another with a concentration at least 3 times of LLOQ in the elimination phase.
- Per bioanalytical report, 97.92% of ISR samples (188 samples) were acceptable and within the acceptance criteria specified in the SOP.

Valsartan

- The ISR was performed on 7.26% (192 samples) of the total number of valsartan samples (2643 samples) per SOP (b)(4). The applicant's ISR sample selection is also consistent with the current Guidance for Industry, *Bioanalytical Method*

Validation (May 2018) described in [Section 4.1.1.3.3.5](#). Per SOP and bioanalytical report, at least one valsartan sample per period per subject was selected around C_{max} concentration and another with a concentration at least 3 times of LLOQ in the elimination phase.

- Per bioanalytical report, 98.44% of ISR samples (189 samples) were acceptable and within the acceptance criteria specified in the SOP.

The bioanalytical portion of the pivotal fed BE study is **adequate**.

4.1.2.4 Pharmacokinetic Results

4.1.2.4.1 Arithmetic Mean Pharmacokinetic Parameters – Assessor Calculated

Sacubitril

REPLICATE 1 (PERIODS 1 AND 2)

Parameter	Unit	Test				Reference				Ratio (T/R)
		Mean	CV%	Min	Max	Mean	CV%	Min	Max	
AUCT	ng.hr/mL	2739.985	16.17	2015.06	4107.06	2689.442	19.68	2009.11	4311.15	1.02
AUCINF	ng.hr/mL	2802.973	16.53	2049.55	4189.79	2745.750	20.83	2038.11	4621.79	1.02
C _{MAX}	ng/mL	1597.231	37.63	667.04	3086.10	1507.715	40.15	706.48	3448.90	1.06
T _{MAX} *	hr	1.670	.	0.50	4.50	1.670	.	0.67	4.50	1.00
KEL	hr-1	0.865	40.70	0.19	1.62	0.943	38.36	0.07	1.46	0.92
THALF	hr	1.019	66.88	0.43	3.65	1.183	157.54	0.48	10.43	0.86

* T_{max} values are presented as median, range

REPLICATE 2 (PERIODS 3 AND 4)

Parameter	Unit	Test				Reference				Ratio (T/R)
		Mean	CV%	Min	Max	Mean	CV%	Min	Max	
AUCT	ng.hr/mL	2759.848	18.92	1774.39	4271.46	2729.409	20.48	1876.02	4339.06	1.01
AUCINF	ng.hr/mL	2837.579	20.04	1821.41	4363.50	2765.307	20.59	1893.29	4430.43	1.03
C _{MAX}	ng/mL	1487.049	43.48	601.94	2851.20	1731.443	42.02	768.55	3092.90	0.86
T _{MAX} *	hr	2.165	.	0.83	10.00	1.670	.	0.67	4.00	1.30
KEL	hr-1	0.817	45.93	0.12	1.48	0.943	30.60	0.31	1.40	0.87
THALF	hr	1.216	90.08	0.47	5.84	0.836	45.60	0.49	2.24	1.45

* T_{max} values are presented as median, range

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ALL PERIODS (PERIODS 1, 2, 3, AND 4)

Parameter	Unit	Test				Reference				Ratio (T/R)
		Mean	CV%	Min	Max	Mean	CV%	Min	Max	
AUCT	ng.hr/mL	2750.097	17.48	1774.39	4271.46	2709.062	19.91	1876.02	4339.06	1.02
AUCINF	ng.hr/mL	2820.276	18.23	1821.41	4363.50	2755.351	20.52	1893.29	4621.79	1.02
C _{MAX}	ng/mL	1541.138	40.32	601.94	3086.10	1617.545	41.51	706.48	3448.90	0.95
T _{MAX} *	hr	1.670	.	0.50	10.00	1.670	.	0.67	4.50	1.00
KEL	hr-1	0.841	42.95	0.12	1.62	0.943	34.45	0.07	1.46	0.89
THALF	hr	1.117	81.34	0.43	5.84	1.013	133.89	0.48	10.43	1.10

* T_{max} values are presented as median, range

Valsartan

REPLICATE 1 (PERIODS 1 AND 2)

Parameter	Unit	Test				Reference				Ratio (T/R)
		Mean	CV%	Min	Max	Mean	CV%	Min	Max	
AUCT	ng.hr/mL	25114.91	36.10	12003.23	51602.20	24453.96	31.73	14195.92	41116.04	1.03
AUCINF	ng.hr/mL	25433.58	35.85	12266.14	52052.54	24778.58	31.28	14360.41	41430.03	1.03
C _{MAX}	ng/mL	3212.174	27.69	1598.00	4620.70	3133.357	27.54	1772.00	5234.30	1.03
T _{MAX} *	hr	3.000	.	1.33	6.00	3.500	.	1.67	5.00	0.86
KEL	hr-1	0.105	23.06	0.07	0.15	0.104	22.50	0.07	0.14	1.00
THALF	hr	6.996	24.11	4.63	10.13	6.966	22.23	4.84	9.46	1.00

* T_{max} values are presented as median, range

REPLICATE 2 (PERIODS 3 AND 4)

Parameter	Unit	Test				Reference				Ratio (T/R)
		Mean	CV%	Min	Max	Mean	CV%	Min	Max	
AUCT	ng.hr/mL	24547.68	19.93	13887.63	30480.54	22072.39	24.34	14543.91	30937.80	1.11
AUCINF	ng.hr/mL	24861.19	19.55	14124.20	30757.82	22449.71	23.91	14857.66	31389.67	1.11
C _{MAX}	ng/mL	3194.979	22.58	1617.20	4929.60	3065.426	26.86	1639.20	4962.20	1.04
T _{MAX} *	hr	4.000	.	2.00	12.00	3.330	.	1.33	4.50	1.20
KEL	hr-1	0.096	19.78	0.07	0.14	0.098	22.67	0.05	0.14	0.98
THALF	hr	7.443	18.28	4.79	10.36	7.441	26.59	5.07	14.58	1.00

* T_{max} values are presented as median, range

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ALL PERIODS (PERIODS 1, 2, 3, AND 4)

Parameter	Unit	Test				Reference				Ratio (T/R)
		Mean	CV%	Min	Max	Mean	CV%	Min	Max	
AUCT	ng.hr/mL	24826.14	28.94	12003.23	51602.20	23284.82	28.95	14195.92	41116.04	1.07
AUCINF	ng.hr/mL	25142.18	28.66	12266.14	52052.54	23635.31	28.47	14360.41	41430.03	1.06
C _{MAX}	ng/mL	3203.420	25.00	1598.00	4929.60	3100.009	26.99	1639.20	5234.30	1.03
T _{MAX} *	hr	3.670	.	1.33	12.00	3.330	.	1.33	5.00	1.10
KEL	hr ⁻¹	0.100	21.79	0.07	0.15	0.102	22.58	0.05	0.14	0.99
THALF	hr	7.223	21.20	4.63	10.36	7.199	24.62	4.84	14.58	1.00

* T_{max} values are presented as median, range

4.1.2.4.2 Geometric Means and 90% Confidence Intervals - Applicant Calculated

Sacubitril and Valsartan tablets 97mg/103 mg (No of subjects completed= 28) Dose (1 X 97mg/103 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fed Bioequivalence Study (Study No. 663/18) (Sacubitril)						
Parameter	Test	N	Reference	N	Ratio (%)	90% C.I.
AUC _t (hr*ng /mL)	2707.465	55	2658.337	55	101.85	98.99-104.79
AUC _{inf} (hr*ng /mL)	2781.480	54	2701.671	55	102.95	100.14-105.85
C _{max} (ng/ml)	1417.070	55	1490.459	55	95.08	83.25-108.59
Fed Bioequivalence Study (Study No. 663/18) (Valsartan)						
Parameter	Test	N	Reference	N	Ratio (%)	90% C.I.
AUC _t (hr*ng /mL)	23898.80	55	22299.16	55	107.17	100.12-114.73
AUC _{inf} (hr*ng /mL)	24223.20	55	22662.43	55	106.89	99.92-114.34
C _{max} (ng/ml)	3101.307	55	2983.297	55	103.96	96.45-112.05

For Sacubitril, AUC_t & AUC_{inf}, the S_{WR} is < 0.294, hence conventional average bioequivalence approach was used for the calculation and the results are represented in bold.

For Valsartan, C_{max}, AUC_t & AUC_{inf}, the S_{WR} is < 0.294, hence conventional average bioequivalence approach was used for the calculation and the results are represented in bold.

Fed Bioequivalence Study (Study No. 663/18) (Sacubitril)								
Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s _{2wr}	s _{WR}	95% Criteria Bound	Method Used	Outcome
LAUCT	101.85	98.99	104.79	0.007	0.08494	-0.002731	MIXED	PASS
LAUCI	102.95	100.14	105.85	0.007	0.08385	-0.001246	MIXED	PASS
LCMAX	95.08	83.25	108.59	0.105	0.32346	-0.031593	MIXED	PASS
Fed Bioequivalence Study (Study No. 663/18) (Valsartan)								

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Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s _{2wr}	s _{WR}	95% Criteria Bound	Method Used	Outcome
LAUCT	107.17	100.12	114.73	0.045	0.21195	-0.010853	MIXED	PASS
LAUCI	106.89	99.92	114.34	0.044	0.20997	-0.011334	MIXED	PASS
LCMAX	103.96	96.45	112.05	0.046	0.21333	-0.018156	MIXED	PASS

For Sacubitril, the $C_{max, SWR}$ is > 0.294 , hence reference-scaled average bioequivalence approach was used for the calculation and the results are represented in bold.

4.1.2.4.3 Geometric Means and 90% Confidence Intervals - Assessor Calculated

Sacubitril and Valsartan Tablet 1 × 97 mg/103 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fed Bioequivalence Study No. 663/18 Sacubitril Unscaled Data							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
AUC _{0-t} (hr.ng/ml)	2707.46	55	2658.34	55	1.02	98.99	104.79
AUC _∞ (hr.ng/ml)	2781.48	54	2701.67	55	1.03	100.14	105.85
C _{max} (ng/ml)	1417.07	55	1490.46	55	0.95	83.25	108.59

Scaled Data								
Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	S ² _{WR}	SWR	Criteria Bound	Method Used	Outcome
LnAUC _{0-t}	1.02	98.99	104.79	0.0072154	0.0849436	-0.002731	Unscaled	PASS
LnAUC _{0-inf}	1.03	100.14	105.85	0.007031	0.0838509	-0.001246	Unscaled	PASS
LnC _{max}	0.93	83.25	108.59	0.1046236	0.3234557	-0.031593	Scaled/PE	PASS

Sacubitril and Valsartan Tablet 1 × 97 mg/103 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasting Bioequivalence Study No. 662/18 Valsartan Unscaled Data							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
AUC _{0-t} (hr.ng/ml)	23898.80	55	22299.16	55	1.07	100.12	114.73
AUC _∞ (hr.ng/ml)	24223.20	55	22662.43	55	1.07	99.92	114.34
C _{max} (ng/ml)	3101.31	55	2983.30	55	1.04	96.45	112.05

Scaled Data								
Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	S ² _{WR}	SWR	Criteria Bound	Method Used	Outcome

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LnAUC_{0-t}	1.08	100.12	114.73	0.0449237	0.211952	-0.010853	Unscaled	PASS
LnAUC_{0-inf}	1.08	99.92	114.34	0.0440856	0.2099657	-0.011334	Unscaled	PASS
LnC_{max}	1.04	96.45	112.05	0.0455111	0.2133333	-0.018156	Unscaled	PASS

4.1.2.4.4 Additional Information for the Study

SWR*	Sacubitril AUC_i: 0.0849 AUC_i: 0.0839 C_{max}: 0.3235 Valsartan AUC_i: 0.2120 AUC_i: 0.2100 C_{max}: 0.2133
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).	Sacubitril ☐ Yes ☒ No Valsartan ☐ Yes ☒ No
Were the subjects dosed in groups? If yes, was the statistical analysis proper? Is reanalysis by assessor necessary?	Sacubitril ☐ Yes ☒ No Valsartan ☐ Yes ☒ No
Are there measurable drug concentrations at 0 hr? If yes, please comment (and take necessary action, if needed).	Sacubitril ☐ Yes ☒ No Valsartan ☐ Yes ☒ No
Are there first measurable drug concentration as C_{max}? If yes, please comment.	Sacubitril ☐ Yes ☒ No Valsartan ☐ Yes ☒ No
Are there C_{max} at the first time point? If yes, is the study (sample) design adequate?	Sacubitril ☐ Yes ☒ No Valsartan ☐ Yes ☒ No

* The assessor used SAS code "Highly Variable 4-way Crossover "HV-RefScale4Period-ver1.SAS" for statistical analysis. This SAS code does not generate results for Root Mean Square Error (RMSE). Therefore, the assessor included S_{WR} values in place of RMSE.

Ratio of AUC_{0-t}/AUC_{0-∞}*

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Treatment	n	Mean	Minimum	Maximum
Sacubitril				
Test	54	0.98	0.85	0.99
Reference	55	0.98	0.90	0.99
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below.	N/A			
Valsartan				
Test	55	0.99	0.97	1.00
Reference	55	0.98	0.96	0.99
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below.	N/A			

* Calculated by the assessor (SAS code HV-RefScale4Period-ver1.SAS does not provide AUC ratio in its output). AUC ratio calculations are provided in Column #11 of PK sheet within the spreadsheet dataset in [Section 4.4.3](#).

Comments on PK Results: Adequate

- This is an IR product. The median T_{max} (range) values reported for sacubitril and valsartan during the pivotal fed BE study were as follows:

Analyte	T_{max} Test (hours)	T_{max} Reference (hours)	Ratio
Sacubitril	1.67 (0.50-10.00)	1.67 (0.67-4.50)	1.00
Valsartan	3.67 (1.33-12.00)	3.33 (1.33-5.00)	1.10

Based on the T/R ratios calculated above for sacubitril and valsartan, the assessor considers the T_{max} for the test and reference products in the pivotal fed BE study comparable (i.e., within 0.80 – 1.25).

- As with the pivotal fasting BE study, the applicant proposed to use either the unscaled average BE procedure or the reference-scaled average BE procedure for analyzing sacubitril and valsartan BE parameters in its study protocol depending on the intra-subject variability (swr) as previously described in the pivotal fasting BE study section.

The SWR was < 0.294 for C_{max} , AUC_t , and AUC_i for valsartan while for sacubitril, SWR was < 0.294 for AUC_t and AUC_i and > 0.294 for C_{max} . Therefore, for valsartan, the applicant used the unscaled average BE procedure, while for sacubitril, the applicant used the unscaled average BE procedure for AUC_t and AUC_i and reference-scaled procedure for C_{max} . According to the clinical study protocol, all evaluable subjects completing at least two periods of the study were included in the statistical analysis.

- The assessor used Highly Variable 4-way Crossover SAS program with SAS code CONTINU to analyze the data (HV-RefScale4Period-ver1.SAS). The SAS programs contained the standard BE approach (unscaled data) and reference scaled BE approach (scaled data). Both scaled and unscaled approach use SAS PROC MIXED procedure. The applicant used SAS PROC MIXED procedure for the evaluation of within-subject variability, which is the same as the assessor's.
- For valsartan, since the S_{WR} was < 0.294 for C_{max} , AUC_t , and AUC_i , the unscaled average BE procedure was used to evaluate the least squares geometric means of C_{max} , AUC_t , and AUC_i . The results of the unscaled data showed that the 90% C.I. values for the least squares geometric means of C_{max} , AUC_t , and AUC_i of valsartan in the pivotal fed BE study were within the acceptable BE limits of 80.00-125.00%.
- For sacubitril, S_{WR} was < 0.294 for AUC_t and AUC_i and > 0.294 for C_{max} . Therefore, the unscaled average BE procedure was used to evaluate the least squares geometric means of AUC_t and AUC_i while reference-scaled procedure was used for C_{max} . The results of the unscaled data showed that the 90% C.I. values for the least squares geometric means of AUC_t and AUC_i of sacubitril in the pivotal fed BE study were within the acceptable BE limits of 80.00-125.00%. The 95% upper confidence bounds for $(\mu_T - \mu_R)^2 - \theta S_{WR}^2$ for C_{max} of sacubitril in the pivotal fed BE study were < 0 , meeting the first condition²⁴. The point estimates (T/R mean ratio) for C_{max} of sacubitril in the pivotal fed BE study were within [0.8, 1.25], meeting the second condition.
- The assessor's analysis for both sacubitril and valsartan are similar to the applicant's results and thus confirmed the applicant's conclusion.

The pharmacokinetic portion of the pivotal fed BE study is **adequate**.

4.1.2.5 Overall Comment

Was the pivotal fed bioequivalence study acceptable? **No**, due to method validation deficiencies.

**Mean Plasma Concentrations, Single-Dose Pivotal Fed Bioequivalence Study -
Assessor Calculated**

Sacubitril					
Time (hr)	Test (n = 54)		Reference (n = 55)		T/R Ratio
	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	
0	0.00	.	0.00	.	-
0.17	59.53	124.02	44.72	166.45	1.33
0.33	267.61	119.91	233.64	124.28	1.15
0.5	403.56	113.41	421.91	133.43	0.96
0.67	492.17	112.61	565.99	134.20	0.87
0.83	583.91	107.07	631.79	122.75	0.92
1	725.33	93.12	710.14	97.04	1.02
1.33	893.92	83.82	962.69	63.29	0.93
1.67	752.20	75.39	996.96	52.56	0.75
2	702.87	56.69	924.46	54.73	0.76
2.33	643.85	66.20	755.17	50.80	0.85
2.67	636.89	73.45	626.13	54.57	1.02
3	507.63	63.24	526.43	72.80	0.96
3.33	428.95	64.76	394.00	67.84	1.09
3.67	350.24	71.81	321.16	67.19	1.09
4	313.23	82.16	275.58	75.10	1.14
4.5	360.13	127.22	233.19	119.02	1.54
5	191.21	117.70	117.20	109.43	1.63
5.5	103.15	108.95	68.36	115.38	1.51
6	71.06	122.76	43.08	126.27	1.65
8	26.86	218.14	9.46	237.67	2.84
10	24.53	363.20	4.39	360.36	5.59
12	10.49	509.75	0.00	.	-

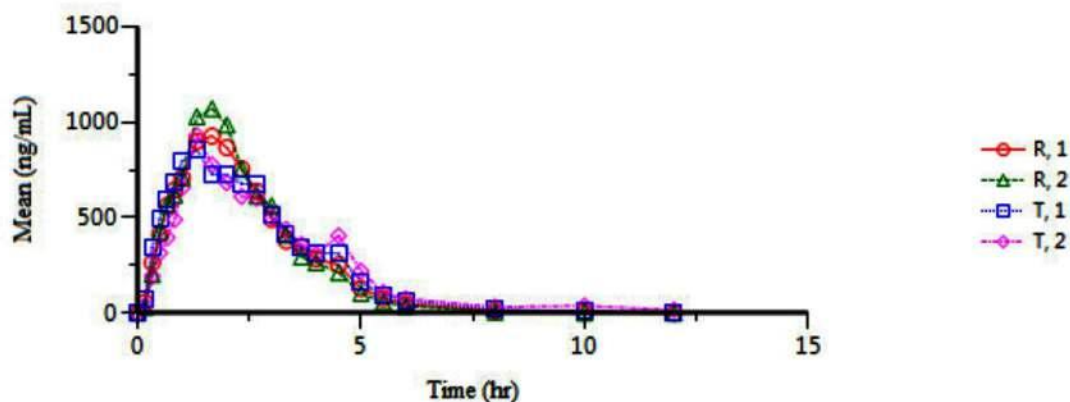
Valsartan					
Time (hr)	Test (n = 55)		Reference (n = 55)		T/R Ratio
	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	
0	0.00	.	0.00	.	-
0.33	222.19	67.72	183.82	62.25	1.21
0.67	532.99	65.45	473.80	69.04	1.12
1	872.63	70.22	883.36	90.93	0.99
1.33	1274.07	66.25	1334.46	76.93	0.95
1.67	1595.94	61.67	1758.14	59.46	0.91
2	1882.27	57.10	2095.52	45.05	0.90
2.33	2038.84	46.84	2333.54	34.27	0.87
2.67	2298.39	39.45	2504.23	27.87	0.92
3	2425.80	35.71	2568.15	25.47	0.94

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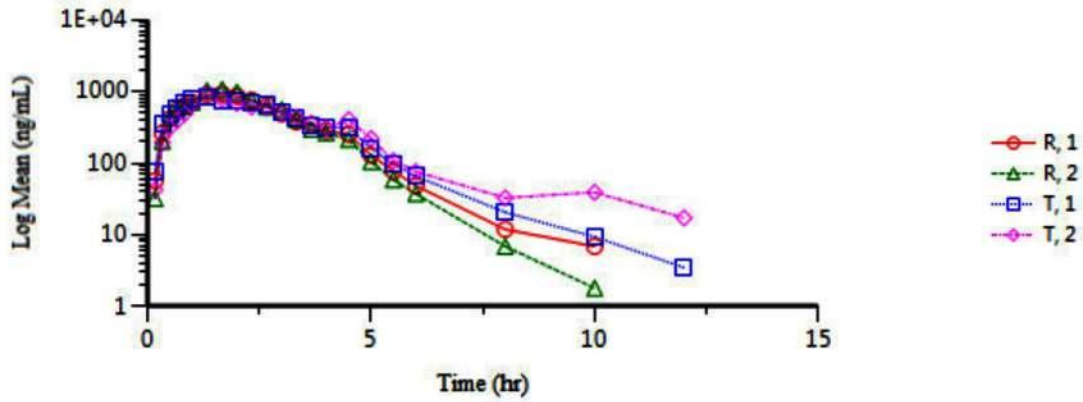
Valsartan					
Time (hr)	Test (n = 55)		Reference (n = 55)		T/R Ratio
	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	
3.33	2555.81	32.30	2610.91	25.36	0.98
3.67	2606.65	32.91	2606.40	27.26	1.00
4	2664.17	33.23	2629.43	27.49	1.01
4.5	2728.97	33.38	2578.53	30.43	1.06
5	2386.47	32.80	2240.91	34.34	1.06
5.5	2060.16	31.26	1921.69	32.73	1.07
6	1878.53	33.38	1725.41	33.27	1.09
8	1329.98	38.50	1228.21	37.42	1.08
10	1041.40	47.02	909.66	43.66	1.14
12	777.71	57.27	671.44	45.84	1.16
16	397.59	61.34	343.41	44.93	1.16
24	147.79	52.51	130.26	42.98	1.13
36	62.57	49.83	53.86	41.66	1.16
48	14.44	98.90	9.83	132.50	1.47

Mean Plasma Concentrations, Single-Dose Pivotal Fed Bioequivalence Study - Assessor Calculated

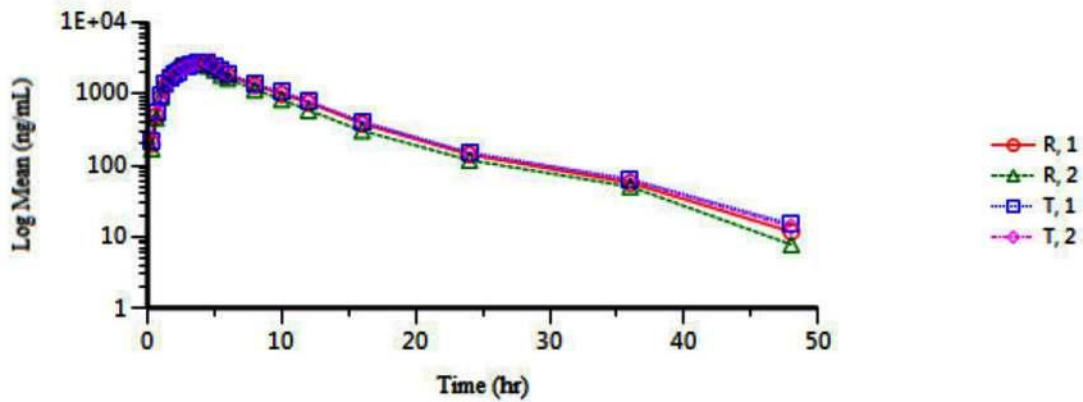
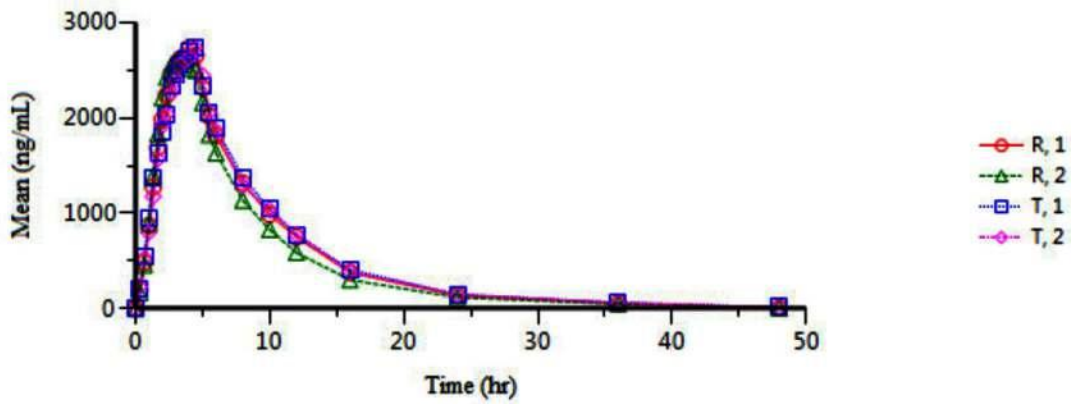
Sacubitril



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Valsartan



4.2 Formulation Data

4.2.1 Test Formulation

Ingredients	Compendial Reference	Pharmaceutical Function	24 mg/ 26 mg	49 mg/ 51 mg	97 mg/ 103 mg	% w/w
			(mg/ Tablet)			
Intra-granular materials						
Sacubitril-Valsartan 3Na Complex [^]	In-House	Active Ingredient	(b)(4)			
Low-substituted hydroxypropylcellulose (b)(4)	USP-NF	(b)(4)				
Microcrystalline Cellulose (b)(4)	USP-NF					
Crospovidone (b)(4)	USP-NF					
Silicon Dioxide (b)(4)	USP-NF					
Magnesium Stearate (b)(4)	USP-NF					
(b)(4)						
Weight of Coated Tablet			103.000	206.000	412.000	100.000

(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.

4.2.2 Inactive Ingredients (IIG Table)

Inactive Ingredients Guide (IIG) Levels					
Component	Amount (mg)/ Tablet	MDI [8 Tablets] (mg)	FDA's IIG Limit (mg, Route of Administration)	IIG Limit Reference	MDI Below or Exceeding FDA's IIG Limit
Low-substituted hydroxy propyl cellulose (b)(4)					(b) (4)
Microcrystalline Cellulose					
Crospovidone (b)(4)					
Silicon Dioxide					
Magnesium Stearate					
(b) (4)					

(b) (4)

(b) (4)

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

Comments on Formulation:

- All inactive ingredients in the formulation are within IIG limit for orally administered products.

- (b) (4)

Per RLD labeling⁶, [t]he safety and effectiveness of ENTRESTO in pediatric heart failure patients 1 to <18 years old are supported by the reduction from baseline to 12 weeks in NT-proBNP in a randomized, double-blind clinical study... Safety and effectiveness have not been established in pediatric patients less than 1 year of age.

²⁸ GS Review: NDA 207620, New/Supplement (Supplement-13 (Efficacy)), 04/01/2019 (Module 3.2.P.1. Description And Composition Of The Drug Product - 50 mg, 100 mg, 200 mg.pdf). Supplement-13 was approved on 10/1/2019 [DARRTS: NDA 207620, COR-SNDACTION-05 (Approval), 10/01/2019]. Per the RLD annual reports, the RLD formulation has not changed since its approval on 7/7/2015.

In addition, regarding renal impairment, *[n]o dose adjustment is required in patients with mild (eGFR 60 to 90 mL/min/1.73 m²) to moderate (eGFR 30 to 60 mL/min/1.73 m²) renal impairment. The recommended starting dose in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m²) is 24/26 mg twice daily.*

(b) (4)

The formulation of the test product is **acceptable** for all strengths.

4.3 Dissolution Testing

4.3.1 Dissolution Data

4.3.1.1 24 mg/26 mg, Sacubitril

Dissolution Conditions		Apparatus: USP - Type II (Paddle)									
Speed of Rotation:		50 RPM									
Medium:		pH 6.8 Phosphate Buffer									
Volume:		900 mL									
Temperature:		37 ± 0.5°C									
Firm's Proposed Specifications											
Not less than $\frac{m}{Q}$ % (Q) of Sacubitril is dissolved in 30 minutes.											
Laurus Labs Limited, Plot No. 19, 20 and 21, Western Sector, APSEZ, Atchutapuram, Visakhapatnam, Andhra Pradesh 531011, 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	
Study Report #: AR/FDFE/165/1218	15-Apr-2019	Sacubitril and Valsartan Tablets 24/26 mg Batch No.: E1801031 Mfg. date: December 2018	24/26 mg Tablets	12	Release of Sacubitril			Module 2.7			
					Mean	63	86		95	98	98
					Range	(b)(4)					
Study Report #: AR/FDFE/166/1218	15-Apr-2019	Sacubitril and Valsartan Tablets 24/26 mg Batch No.: E1801131 Mfg. date: December 2018	24/26 mg Tablets	12	Mean	7.1	6.4	4.5	3.6	3.0	
					Range	(b)(4)					
					%CV	59	80	94	97	97	
Study Report #: AR/FDFE/167/1218	15-Apr-2019	Sacubitril and Valsartan Tablets 24/26 mg Batch No.: E180121 Mfg. date: December 2018	24/26 mg Tablets	12	Mean	9.6	7.2	3.1	1.5	1.5	
					Range	(b)(4)					
					%CV	56	78	94	97	98	
Study	20-Apr-2019	Entresto (Sacubitril and Valsartan) 24/26 mg Lot No.: FX000197	24/26 mg Tablets	12	Mean	11.0	11.2	6.1	3.9	4.7	
					Range	(b)(4)					
					%CV	65	91	94	95	96	
					Mean	9.6	8.0	2.9	1.8	1.6	
					Range	(b)(4)					
					%CV	9.6	8.0	2.9	1.8	1.6	

Report #: AR/FDFE/155/ 1218	Expiry date: October 2020								

4.3.1.2 24 mg/26 mg, Valsartan

Dissolution Conditions		Apparatus:		USP - Type II (Paddle)							
Speed of Rotation:		50 RPM									
Medium:		pH 6.8 Phosphate Buffer									
Volume:		900 mL									
Temperature:		37 ± 0.5°C									
Firm's Proposed Specifications		Not less than $\frac{100}{Q}\%$ (Q) of Valsartan is dissolved in 30 minutes.									
Dissolution Testing Site (Name, Address)		Laurus Labs Limited, Plot No. 19, 20 and 21, Western Sector, APSEZ, Atchutapuram, Visakhapatnam, Andhra Pradesh 531011, India.									
Study Report #:	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	
Study Report #: AR/FDFE/165/1218	15-Apr-2019	Sacubitril and Valsartan Tablets 24/26 mg Batch No.: E1801031 Mfg. date: December 2018	24/26 mg Tablets	12	Release of Valsartan			Module 2.7			
					Mean	62	85		94	96	97
					Range	(b)(4)					
Study Report #: AR/FDFE/166/1218	15-Apr-2019	Sacubitril and Valsartan Tablets 24/26 mg Batch No.: E1801131 Mfg. date: December 2018	24/26 mg Tablets	12	%CV	9.3	7.0	3.1	1.5	1.5	
					Mean	59	81	94	97	97	
					Range	(b)(4)					
Study Report #: AR/FDFE/167/1218	15-Apr-2019	Sacubitril and Valsartan Tablets 24/26 mg Batch No.: E1801211 Mfg. date: December 2018	24/26 mg Tablets	12	%CV	10.5	10.9	5.9	3.7	4.6	
					Mean	56	78	94	96	97	
					Range	(b)(4)					
Study Report #: AR/FDFE/155/1218	20-Apr-2019	Entresto (Sacubitril and Valsartan) 24/26 mg Lot No.: FX000197	24/26 mg Tablets	12	%CV	9.2	7.7	2.8	1.7	1.6	
					Mean	66	91	94	96	96	
					Range	(b)(4)					
%CV	6.6	6.0	4.2	3.3	2.7						

	Expiry date: October 2020								

4.3.1.3 49 mg/51 mg, Sacubitril

Dissolution Conditions		Apparatus:	USP - Type II (Paddle)								
		Speed of Rotation:	50 RPM								
		Medium:	pH 6.8 Phosphate Buffer								
		Volume:	900 mL								
		Temperature:	37 ± 0.5°C								
Firm's Proposed Specifications		Not less than $\frac{m}{Q}$ % (Q) of Sacubitril is dissolved in 30 minutes.									
Dissolution Testing Site (Name, Address)		Laurus Labs Limited, Plot No. 19, 20 and 21, Western Sector, APSEZ, Atchutapuram, Visakhapatnam, Andhra Pradesh 531011, 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	
Study Report #: AR/FDF/161/1218	15-Apr-2019	Sacubitril and Valsartan Tablets 49/51 mg Batch No.: EI801011 Mfg. date: December 2018	49/51 mg Tablets	12	Release of Sacubitril				Module 2.7		
					Mean	62	85	96		97	98
					Range	(b)(4)					
Study Report #: AR/FDF/163/1218	15-Apr-2019	Sacubitril and Valsartan Tablets 49/51 mg Batch No.: EI801111 Mfg. date: December 2018	49/51 mg Tablets	12	%CV	10.2	6.9	4.5	2.7	1.5	
					Mean	58	80	93	97	98	
					Range	(b)(4)					
Study Report #: AR/FDF/164/1218	15-Apr-2019	Sacubitril and Valsartan Tablets 49/51 mg Batch No.: EI801221 Mfg. date: December 2018	49/51 mg Tablets	12	%CV	11.1	9.2	7.2	4.1	2.0	
					Mean	57	77	89	95	97	
					Range	(b)(4)					
Study Report #: AR/FDF/156/1218	20-Apr-2019	Entresto (Sacubitril and Valsartan) 49/51 mg Lot No.: FX000155 Expiry date: September 2020	49/51 mg Tablets	12	%CV	8.6	9.3	8.2	4.2	2.2	
					Mean	57	76	86	93	95	
					Range	(b)(4)					
		%CV	10.4	7.6	5.3	3.0	2.4				

4.3.1.4 49 mg/51 mg, Valsartan

Apparatus:		USP - Type II (Paddle)								
Speed of Rotation:		50 RPM								
Medium:		pH 6.8 Phosphate Buffer								
Volume:		900 mL								
Temperature:		37 ± 0.5°C								
Firm's Proposed Specifications										
Not less than $\frac{m}{Q}$ % (Q) of Valsartan is dissolved in 30 minutes.										
Laurus Labs Limited, Plot No. 19, 20 and 21, Western Sector, APSEZ, Atchutapuram, Visakhapatnam, Andhra Pradesh 531011, India.										
Dissolution Conditions										
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		
Study Report #: AR/FDFE/161/1218	15-Apr-2019	Sacubitril and Valsartan Tablets 49/51 mg Batch No.: E1801011 Mfg. date: December 2018	49/51 mg Tablets	12	10	15	20	30	45	
					Release of Valsartan					
Study Report #: AR/FDFE/163/1218	15-Apr-2019	Sacubitril and Valsartan Tablets 49/51 mg Batch No.: E1801111 Mfg. date: December 2018	49/51 mg Tablets	12	Mean	61	84	94	96	96
					Range	(b)(4)				
Study Report #: AR/FDFE/164/1218	15-Apr-2019	Sacubitril and Valsartan Tablets 49/51 mg Batch No.: E1801221 Mfg. date: December 2018	49/51 mg Tablets	12	%CV	10.0	6.8	4.3	2.5	1.5
					Mean	58	81	93	97	98
Study Report #: AR/FDFE/156/1218	20-Apr-2019	Entresto (Sacubitril and Valsartan) 49/51 mg Lot No.: FX000155 Expiry date: September 2020	49/51 mg Tablets	12	Range	(b)(4)				
					%CV	10.9	9.0	7.0	3.8	1.9
Study Report #: AR/FDFE/164/1218	15-Apr-2019	Sacubitril and Valsartan Tablets 49/51 mg Batch No.: E1801221 Mfg. date: December 2018	49/51 mg Tablets	12	Mean	57	77	88	94	96
					Range	(b)(4)				
Study Report #: AR/FDFE/164/1218	15-Apr-2019	Sacubitril and Valsartan Tablets 49/51 mg Batch No.: E1801221 Mfg. date: December 2018	49/51 mg Tablets	12	%CV	8.4	9.1	7.9	3.9	2.1
					Mean	58	77	87	94	96
Study Report #: AR/FDFE/156/1218	20-Apr-2019	Entresto (Sacubitril and Valsartan) 49/51 mg Lot No.: FX000155 Expiry date: September 2020	49/51 mg Tablets	12	Range	(b)(4)				
					%CV	10.2	7.4	5.1	2.9	2.3

[Module 2.7](#)

4.3.1.5 97 mg/103 mg, Sacubitril

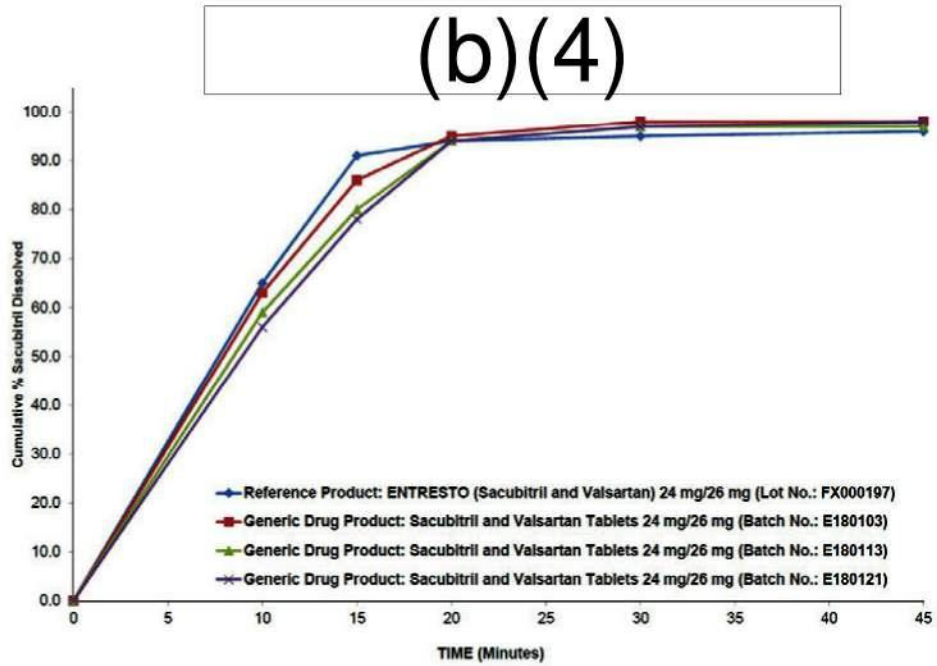
Apparatus:		USP - Type II (Paddle)							
Speed of Rotation:		50 RPM							
Medium:		pH 6.8 Phosphate Buffer							
Volume:		900 mL							
Temperature:		37 ± 0.5°C							
Firm's Proposed Specifications									
Not less than $\frac{Q}{Q}$ % (Q) of Sacubitril is dissolved in 30 minutes.									
Dissolution Testing Site (Name, Address)									
Laurus Labs Limited, Plot No. 19, 20 and 21, Western Sector, APSEZ, Atchutapuram, Visakhapatnam, Andhra Pradesh 531011, 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
Study Report #: AR/FIP/1604/1117	15-Apr-2019	Sacubitril and Valsartan Tablets 97/103 mg Batch No.: E180102 Mfg. date: December 2018	97/103 mg Tablets	12	Release of Sacubitril				
					Mean	53	73	88	94
Study Report #: AR/FIP/1707/1217	15-Apr-2019	Sacubitril and Valsartan Tablets 97/103 mg Batch No.: E180112 Mfg. date: December 2018	97/103 mg Tablets	12	(b)(4)				
					%CV	2.0	2.5	4.2	3.6
Study Report #: AR/FIP/1792/1217	15-Apr-2019	Sacubitril and Valsartan Tablets 97/103 mg Batch No.: E180123 Mfg. date: December 2018	97/103 mg Tablets	12	(b)(4)				
					%CV	2.3	3.4	2.0	0.8
Study Report #: AR/FDE/155/1218	17-Apr-2019	Entresto (Sacubitril and Valsartan) 97/103 mg Lot No.: FX000079 Expiry date: July 2020	97/103 mg Tablets	12	(b)(4)				
					%CV	65	82	94	97
					Module 2.7				
					15.2	12.8	8.4	3.3	1.9

4.3.1.6 97 mg/103 mg, Valsartan

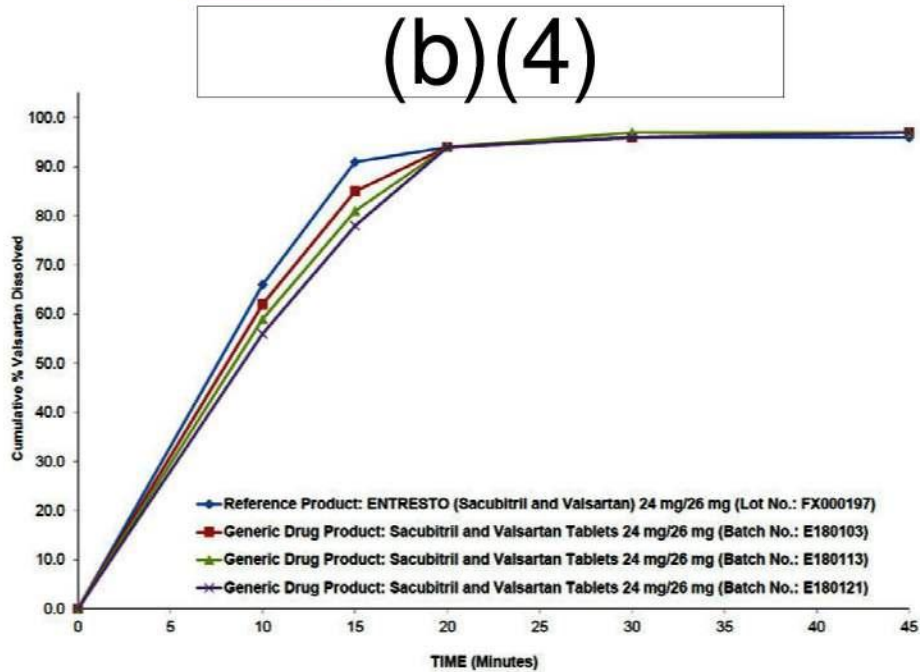
Apparatus:		USP - Type II (Paddle)									
Speed of Rotation:		50 RPM									
Medium:		pH 6.8 Phosphate Buffer									
Volume:		900 mL									
Temperature:		37 ± 0.5°C									
Firm's Proposed Specifications		Not less than $\frac{m}{Q}$ % (Q) of Valsartan is dissolved in 30 minutes.									
Dissolution Testing Site (Name, Address)		Laurus Labs Limited, Plot No. 19, 20 and 21, Western Sector, APSEZ, Atchutapuram, Visakhapatnam, Andhra Pradesh 531011, 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	
Study Report #: AR/FDFE/151/1218	15-Apr-2019	Sacubitril and Valsartan Tablets 97/103 mg Batch No.: E1801021 Mfg. date: December 2018	97/103 mg Tablets	12	Release of Valsartan					Module 2.7	
					Mean	52	72	87	93		94
					Range	(b)(4)					
Study Report #: AR/FDFE/153/1218	15-Apr-2019	Sacubitril and Valsartan Tablets 97/103 mg Batch No.: E1801121 Mfg. date: December 2018	97/103 mg Tablets	12	%CV	2.0	2.5	4.1	3.4	2.0	
					Mean	54	75	91	96	97	
					Range	(b)(4)					
Study Report #: AR/FDFE/158/1218	15-Apr-2019	Sacubitril and Valsartan Tablets 97/103 mg Batch No.: E1801231 Mfg. date: December 2018	97/103 mg Tablets	12	%CV	2.2	3.4	2.0	0.8	0.7	
					Mean	64	82	93	96	96	
					Range	(b)(4)					
Study Report #: AR/FDFE/157/1218	17-Apr-2019	Entresto (Sacubitril and Valsartan) 97/103 mg Lot No.: FX000079 Expiry date: July 2020	97/103 mg Tablets	12	%CV	5.6	4.0	3.7	2.4	1.9	
					Mean	53	73	87	95	96	
					Range	(b)(4)					
%CV	15.0	12.7	8.3	3.2	1.8						

4.3.2 Dissolution Profiles

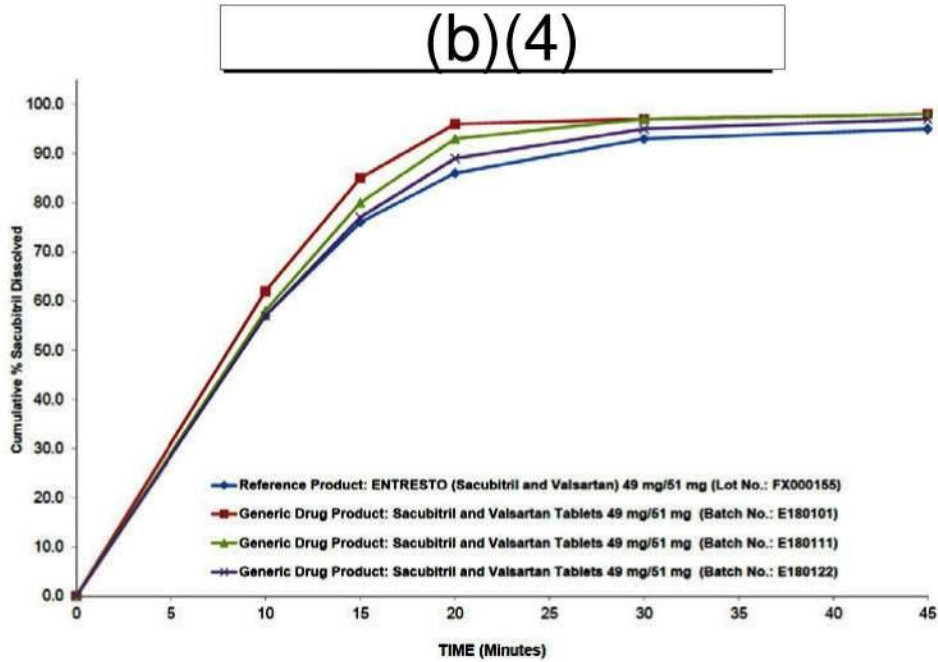
4.3.2.1 24 mg/26 mg, Sacubitril



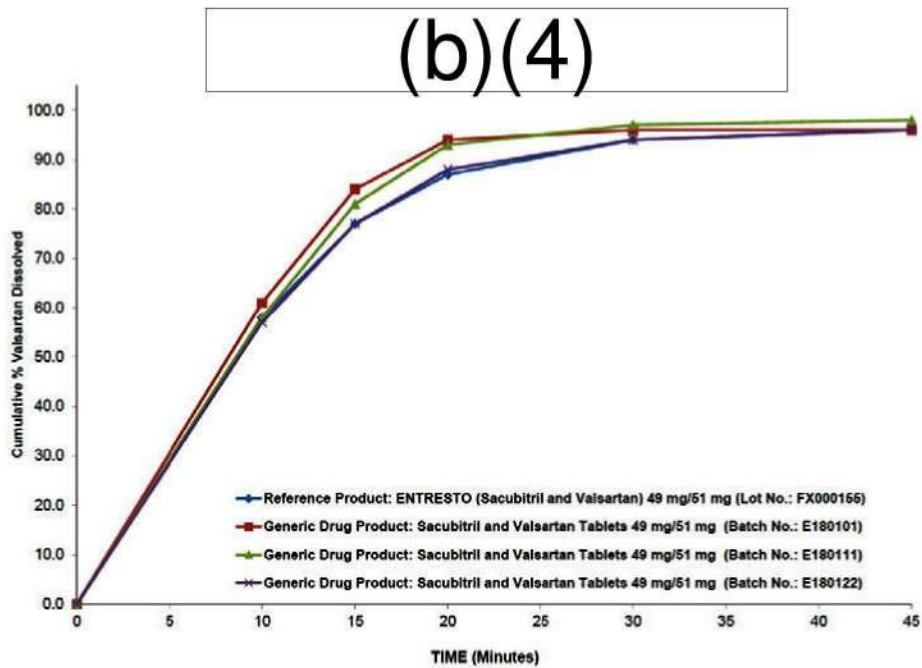
4.3.2.2 24 mg/26 mg, Valsartan



4.3.2.3 49 mg/51 mg, Sacubitril

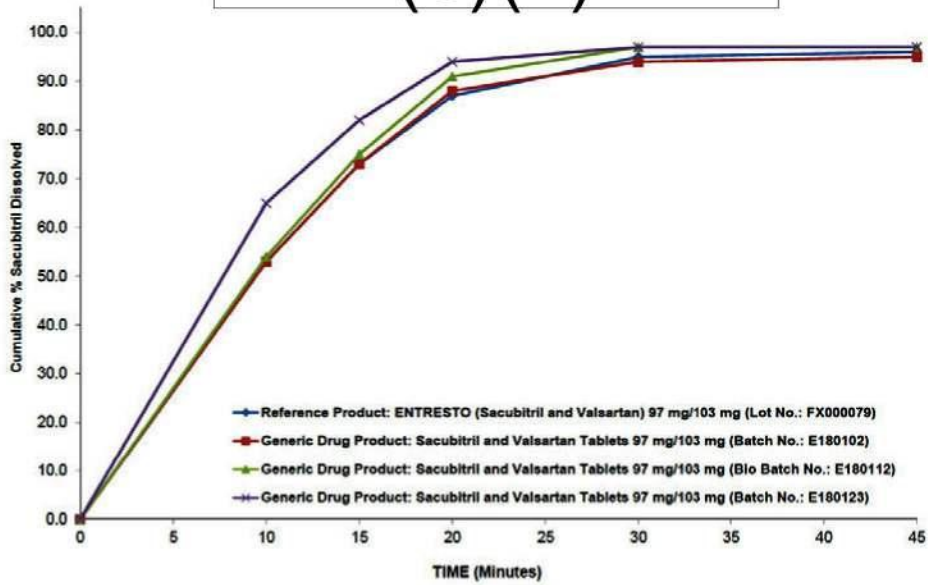


4.3.2.4 49 mg/51 mg, Valsartan



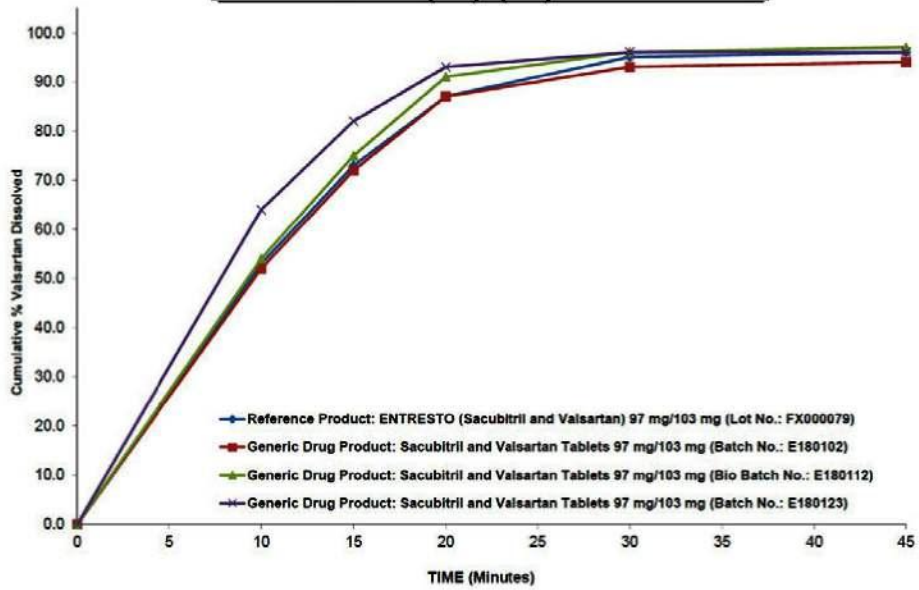
4.3.2.5 97 mg/103 mg, Sacubitril

(b)(4)



4.3.2.6 97 mg/103 mg, Valsartan

(b)(4)



4.3.3 F2 Metric

F2 metric calculated?	☐ Yes ☒ No
If no, reason why F2 not calculated	Rapid dissolution (> 85% in < 30 min).

Please comment on whether dissolution data are adequate to support requests submitted under 21 CFR 320.22(d)(2) or 320.24(b)(6).	Adequate Per 21 CFR 320.22(d)(2)

Overall Comments: Adequate

- The biopharmaceutics assessment is pending as of 12/12/2019. There is no USP method for this drug product but there is an FDA-recommended dissolution method [900 mL of Phosphate Buffer, pH 6.8 (b)(4) using USP Apparatus I (Paddle) at 75 rpm]. The applicant conducted comparative dissolution testing using the FDA-recommended dissolution method (b)(4). The assessor notes that the FDA-recommended dissolution method was revised on 10/24/2019 after submission of the current ANDA. In the applicant's pharmaceutical development report, the applicant conducted dissolution testing on prototype test batches using the FDA-recommended dissolution method (b)(4) (b)(4) (b)(4). The dissolution method and specification for quality control purposes will be assessed separately in the biopharmaceutics assessment.
- For each strength of the test product, the applicant provided the results of in vitro dissolution testing for 3 lots of test product and one lot of reference product, including the bio lots used during the in vivo pivotal fasting and fed BE studies, using the FDA-recommended dissolution method. The in vitro dissolution testing on the test lots was performed within 4 months from the date of the manufacture. The reference lots were not expired at the time of dissolution testing.
- For all strengths of the drug product, the applicant provided the comparative dissolution data for the test and reference products. Based on the mean dissolution data, both the test and reference products showed (b)(4) dissolution profiles (b)(4) % drug release (b)(4).
- Considering that the biopharmaceutics assessment of the applicant's proposed dissolution method and specification is currently pending, the assessment of waiver requests for the lower strengths 24 mg/26 mg and 49 mg/51 mg of the test product will be completed based on the acceptance of applicant's proposed dissolution method.

²⁹ GS Review: ANDA 213676, New/ANDA, 07/08/2019 (Module 3.2.P.2. Pharmaceutical Development Report.pdf, p. 103 of 113).

Therefore, at this time, the dissolution data are **inadequate** to support waiver request for the 24 mg/26 mg and 49 mg/51 mg strengths of the test product due to outstanding deficiencies and pending the completion of biopharmaceutics assessment.

4.4 Attachments

4.4.1 Additional Studies

Are there any additional studies? (e.g. pilot, failed) If yes, please provide the location of report (complete/summary).	☒ Yes ☐ No <u>Failed Pilot Fasting BE Study No. 060/18:</u> Module 2.7. <u>Failed Pilot Fed BE Study No. 059/18:</u> Module 2.7.
Number of Subjects	<u>Pilot Fasting BE Study No. SLS-CL-0093-17:</u> 20 Subjects enrolled and 18 completed. <u>Failed Pilot Fed BE Study No. SLS-CL-0094-17:</u> 14 Subjects enrolled and 12 completed.
Are the test formulations in the pilot/failed studies and pivotal studies similar ³⁰ ?	☒ Yes ☐ No
What was the objective of pilot/failed study?	To evaluate the performance of prototype formulation of the test product in vivo.
Please comment on reason(s) of failure.	The results of the pilot fasting and fed BE studies failed to meet the BE acceptance limits of 80.00-125.00% due to high intra-subject variability.
Any serious adverse events or deaths reported?	☐ Yes ☒ No

4.4.2 BE Summary Tables for the Additional Studies

4.4.2.1 Failed Pilot Fasting BE Study No. 060/18

4.4.2.1.1 Submission Summary

Drug Product Name	Sacubitril and Valsartan tablets
Strength(s)	97mg/103 mg
Applicant Name	Laurus labs Limited, India
Address	Laurus Labs Limited Second Floor, Serene Chambers, Road No.7, Banjara Hills, Hyderabad, Rangareddy – 500034, India Phone: +91-40-39804333 Fax +91-40-39804320
Point of Contact Name Address	Dr. José D. Gomes, Ph.D., President PharmaQ, Inc. Waterview Plaza, 2001 Route 46, Suite 105, Parsippany, NJ 07054-1315.
Telephone Number Fax Number	(973) 402-5300 (973) 368-1145

³⁰ [Submission of Summary Bioequivalence Data for Abbreviated New Drug Applications](#)

E-mail	jgomes@pharmaq.net / pharmaq@pharmaq.net

4.4.2.1.2 Study Information

Study Number	060/18		
Study Title	An open label, balanced, randomized, two-treatment, four-period, two-sequence, single dose, crossover, full-replicate, oral bioequivalence study of Sacubitril and Valsartan tablets 97 mg/103 mg of Laurus Labs Limited, India comparing with ENTRESTO™ (sacubitril / valsartan) tablets 97mg/103 mg of Novartis Pharmaceuticals Corporation East Hanover, New Jersey 07936 in healthy, adult, human subjects under fasting conditions		
Study Type	☒ In Vivo BE	☐ In Vitro BE	☐ Permeability ☐ Other (Specify)
Submission Location: Study Report	NA		
Validation Report	NA		
Bioanalytical Report	NA		
Clinical Site (Name, Address, Phone #, Fax #)	QPS Bioserve India Pvt. Limited, # 6-56/6/1A, Opp: IDPL Factory, Balanagar, Hyderabad-500 037, Telangana, India. Tel: +91-40-4377 0873 / 1875 Fax: +91-40-4377 0877		
Principal Clinical Investigator (Name, Email)	Dr. K.Babji babji.kalmanoor @qpsbioserve.com		
Analytical Site (Name, Address, Phone #, Fax #)	(b)(4)		
Principal Analytical Investigator (Name, Email)			
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)	(11/09/2018 to 17/10/2018) 37 days -20°C ± 10°C		
Long-Term Storage Stability (LTSS) Coverage (no. days @ temp °C)	147 days @ -20°C ± 10°C and -70° ± 15°C		
LTSS Data Location	NA		

4.4.2.1.3 Product Information

Product	Test		Reference	
Treatment ID	T		R	
Product Name	Sacubitril and Valsartan tablets 97mg/103 mg		ENTRESTO™ (sacubitril / valsartan) tablets 97mg/103 mg	
Manufactured by	Laurus Labs Limited, India		--	
Distributed by	--		Novartis Pharmaceuticals Corporation East Hanover, New Jersey 07936	
Batch No/Lot No	15140-A-044		FX000079	
Manufacture Date	Aug-2018		NA	
Expiration Date	Jan-2019		Jul-2020	
Strength	97mg/103 mg		97mg/103 mg	
Dosage Form	Tablet		Tablet	
Bio-batch Size	(b)(4)		N.A	
Production Batch Size			N.A	
Potency	Sacubitril	99.2%	Sacubitril	101.3%
	Valsartan	100.0%	Valsartan	101.2%
Content Uniformity (mean, %CV)	Sacubitril	2.7	Sacubitril	2.1
	Valsartan	2.7	Valsartan	2.1
Dose Administered	1x 97mg/103 mg		1x 97mg/103 mg	
Route of Administration	Oral		Oral	

4.4.2.1.4 Summary of Bioavailability Studies

Sacubitril

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range))	Mean Parameters +/-SD (%CV) for Sacubitril							Study Report Location
					C _{max} (ng/mL)	T _{max} (hr) Median (Range)	AUC _t (hr*ng/mL)	AUC _{inf} (hr*ng/mL)	t _{1/2} (hr)	k _{el} (hr ⁻¹)	AUC% Extrap	
060/18	To assess the bioequivalence of Sacubitril and Valsartan tablets 97mg/103 mg of Laurus Labs Limited, India comparing with that of ENTRESTO™ (sacubitril / valsartan) tablets 97mg/103 mg of Novartis Pharmaceuticals Corporation East Hanover, New Jersey 07936 in healthy, adult, human subjects under fasting conditions. To monitor adverse events and ensure the safety and tolerability of subjects	An open label, balanced, randomized, two-treatment, four-period, two-sequence, single dose, crossover, full-replicate, oral bioequivalence study in healthy, adult, human subjects under fasting conditions.	Test product (T) 01 tablet	20 Healthy, adult, male, human subjects Age: 31.7 (21.0 - 40.0)	4719.5 ± 2002.4 (42.429)	0.83 (0.33 - 4.00)	6249.923 ± 2454.966 (39.280)	6272.940 ± 2456.825 (39.165)	0.92 ± 0.32 (34.35)	0.8452 ± 0.2923 (34.5822)	0.406 ± 0.161 (39.705)	NA
			Reference product (R): 01 tablet		5553.9 ± 2402.7 (43.261)	0.50 (0.33 - 2.00)	6309.640 ± 2271.699 (36.004)	6331.660 ± 2271.165 (35.870)	0.91 ± 0.24 (26.58)	0.8213 ± 0.2342 (28.5202)	0.390 ± 0.163 (41.634)	

Valsartan

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range))	Mean Parameters +/-SD (%CV) for Valsartan							Study Report Location n
					C _{max} (ng/mL)	T _{max} (hr) Median (Range)	AUC _t (hr*ng/mL)	AUC _{inf} (hr*ng/mL)	t _{1/2} (hr)	k _{el} (hr ⁻¹)	AUC% Extrap	
060/18	To assess the bioequivalence of Sacubitril and Valsartan tablets 97mg/103 mg of Laurus Labs Limited, India comparing with that of ENTRESTO™ (sacubitril / valsartan) tablets 97mg/103 mg of Novartis Pharmaceuticals Corporation East Hanover, New Jersey 07936 in healthy, adult, human subjects under fasting conditions.	An An open label, balanced, randomized, two-treatment, four-period, two-sequence, single dose, crossover, full-replicate, oral bioequivalence study in healthy, adult, human subjects under fasting conditions.	Test product (T): 01 tablet Sacubitril and Valsartan tablet 97mg/103 mg Administered orally Batch No. 15140-A-044	20 Healthy, adult, male, human subjects Age: 30.9 (21-40)	3771.9 ± 1345.2 (35.663)	2.00 (1.00 – 4.00)	27121.61 ± 12295.84 (45.336)	27448.333 ± 12475.112 (45.449)	6.81 ± 1.56 (22.97)	0.1074 ± 0.0259 (24.0905)	1.277 ± 0.718 (56.179)	NA
			Reference product (R): 01 tablet ENTRESTO™ (sacubitril / valsartan) tablet 97mg/103 mg Administered orally Lot Number: FX000079		3935.0 ± 1287.3 (32.714)	2.00 (1.33 – 4.50)	26775.83 ± 11430.10 (42.688)	27109.691 ± 11570.664 (42.681)	7.12 ± 1.50 (21.10)	0.1017 ± 0.0213 (20.9692)	1.304 ± 0.587 (45.039)	

4.4.2.1.5 Statistical Summary of the Comparative Bioavailability Data

Reference Scaled Average Bioequivalence Approach Used					☒ Yes ☐ No	
If No, then complete Table 3A only If Yes, then complete Tables 3A and 3B						
Sacubitril and Valsartan tablets 97mg/103 mg (No of subjects completed= 20) Dose (1 X 97mg/103 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fasting Bioequivalence Study (Study No. 060/18) (Sacubitril)						
Parameter	Test	N	Reference	N	Ratio (%)	90% C.I.
AUC _t (hr*ng /mL)	5760.197	38	5963.343	40	95.88	92.16 - 101.24
AUC _{inf} (hr*ng /mL)	5784.173	38	5986.719	40	95.91	92.20 - 101.24
C _{max} (ng/ml)	4344.789	38	5107.160	40	82.12	74.07 - 97.72
Fasting Bioequivalence Study (Study No. 060/18) (Valsartan)						
Parameter	Test	N	Reference	N	Ratio (%)	90% C.I.
AUC _t (hr*ng /mL)	23751.89	38	24305.17	40	96.06	85.54 - 111.64
AUC _{inf} (hr*ng /mL)	24056.85	38	24626.61	40	96.04	85.66 - 111.41
C _{max} (ng/ml)	3424.471	38	3719.109	40	90.47	79.85 - 106.18

Fasting Bioequivalence Study (Study No. 060/18) (Sacubitril)								
Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	95% Criteria Bound	Method Used	Outcome
LAUCT	95.88	92.16	101.24	0.015	0.12253	-.003623587	GLM	PASS
LAUCI	95.91	92.20	101.24	0.015	0.12175	-.003576393	GLM	PASS
LCMAX	82.12	74.07	97.72	0.150	0.38758	0.008185886	GLM	FAIL
Fasting Bioequivalence Study (Study No. 060/18) (Valsartan)								
Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	Outcome
LAUCT	96.06	85.54	111.64	0.089	0.29892	-0.033429	GLM	PASS
LAUCI	96.04	85.66	111.41	0.088	0.29620	-0.032934	GLM	PASS
LCMAX	90.47	79.85	106.18	0.082	0.28570	0.001875	GLM	FAIL

4.4.2.1.6 Bioanalytical Method Validation

Information Requested	Data
Bioanalytical method validation report location	NA
Analyte	Sacubitril and Valsartan
Internal standard (IS)	Sacubitril 13C4 and Valsartan -D9

Information Requested	Data	
Method description	(b)(4)	
Limit of quantitation	Valsartan	Sacubitril
	14.042 ng/mL	10.021 ng/mL
Average recovery of drug (%)	61.9	64.5
Average recovery of IS (%)	82.1	84.1
Standard curve concentrations range (ng/mL)	14.042 to 7041.0	10.021 to 5024.6
QC Concentrations (ng/mL)	LLOQ QC: 14.079	LLOQ QC: 10.047
	LQC : 36.474	LQC : 26.029
	AQC: 1402.8	AQC: 1001.1
	MQC: 2805.7	MQC: 2002.2
	HQC: 5323.8	HQC: 3799.2
QC Intraday precision range (%)	Valsartan	Sacubitril
	LLOQ QC: 1.4 to 3.4	LLOQ QC: 2.4 to 3.8
	LQC: 0.6 to 1.3	LQC: 1.5 to 4.2
	AQC: 0.6 to 1.2	AQC: 0.6 to 2.0
	MQC: 0.7 to 1.3	MQC: 1.3 to 1.6
HQC: 1.2 to 1.3	HQC: 0.5 to 2.2	
QC Intraday accuracy range (%)	LLOQ QC: 97.7 to 103.2	LLOQ QC: 97.1 to 100.1
	LQC: 92.9 to 94.7	LQC: 94.2 to 97.2
	AQC: 95.6 to 96.8	AQC: 96.1 to 98.0
	MQC: 98.2 to 98.6	MQC: 97.0 to 99.6
	HQC: 98.7 to 99.5	HQC: 96.4 to 97.3
QC Inter day precision (%)	LLOQ QC: 3.4	LLOQ QC: 3.1

Information Requested	Data	
	LQC: 1.3	LQC: 2.9
	AQC: 1.1	AQC: 1.6
	MQC:1.0	MQC: 1.7
	HQC: 1.2	HQC: 1.4
QC Inter day accuracy (%)	LLOQ QC: 100.4	LLOQ QC: 98.2
	LQC: 94.1	LQC: 95.6
	AQC: 96.2	AQC: 97.3
	MQC: 98.3	MQC: 98.1
	HQC: 99.1	HQC: 96.8
Bench-top stability (hrs)	25 hrs 30 mins @ bench top (room temperature) condition	
Stock stability (days)	8 days @ -20°C ± 10°C	
Processed stability (hrs)	144 hrs @ auto sampler temperature (5°C)	
Freeze-thaw stability (cycles)	Five Cycles @ -20°C ± 10°C and -70°C ± 15°C	
Long term storage stability (days)	147 days @ -20°C ± 10°C and -70°C ± 15°C	
Dilution Integrity	Concentration diluted 1/5 th and 1/10 th fold	
Selectivity	No interference peaks noted in blank plasma samples.	

4.4.2.1.7 Formulation Data

S. No	Ingredient	Strength	24mg/26mg	49mg/51mg	97mg/103mg
		% w/w	mg/Tab		
		(b)(4)			
1	Sacubitril-Valsartan 3Na Complex				
2	Low-substituted hydroxypropylcellulose (b)(4)				
3	Microcrystalline Cellulose (b)(4) (b)(4)				
4	Crospovidone Type-A (b)(4) (b)(4)				
5	Silicon dioxide (b)(4)				
6	Magnesium Stearate (b)(4)				

(b)(4)

(b)(4)

Coated tablet weight	–	103.00	206.00	412.00

4.4.2.1.8 Demographic Profile of Subjects Completing the Bioequivalence Study

Study No.: 060/18				
		Treatment Groups		
		Test Product (T) N=20	Reference Product (R) N=20	
Age (years)	Mean ± SD	31.7 ± 6.4	31.7 ± 6.4	
	Range	21.0 – 40.0	21.0 – 40.0	
Age Groups	< 18	00	00	
	18 – 40	20 (100.0%)	20 (100.0%)	
	41 – 64	00	00	
	65 – 75	00	00	
	> 75	00	00	
Sex	Male	20 (100.0%)	20 (100.0%)	
	Female	00	00	
Race	Asian	20 (100.0%)	20 (100.0%)	
	Black	00	00	
	Caucasian	00	00	
	Hispanic	00	00	
	Other	00	00	
BMI	Mean ± SD	23.6 ± 1.7	23.6 ± 1.7	
	Range	19.1 – 24.8	19.1 – 24.8	
Other Factors		NA	NA	

4.4.2.1.9 Dropout Information

Study No. 060/18				
Subject No	Reason for dropout/replacement	Period	Replaced?	Replaced with
(b)(6)	Subject was withdrawn from period-III as he did not turn up for period-III check-in	III	No	NA
	He was withdrawn on (b)(6)			
	Subject was withdrawn from period-II as he did not turn up for period-II check-in	II	No	NA
	He was withdrawn on (b)(6)			

4.4.2.1.10 Incidence of Adverse Events in Individual Studies

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Fasting Bioequivalence Study Study No.: 060/18	
	Test (T) N=20	Reference (R) N=20
Gastrointestinal disorders		
Diarrhea	--	01(5.00%)
Vomiting	--	01(5.00%)
Skin and subcutaneous tissue disorders		
Rash over the abdomen	01(5.00%)	--
Rash over the body	01(5.00%)	--
Musculoskeletal and connective tissue disorders		
Body pains	01(5.00%)	--
Investigations		
Decreased orthostatic diastolic blood pressure	01(5.00%)	--

4.4.2.1.11 Protocol Deviations

Study No.: 060/18		
Type	Subject #s (Test T)	Subject #s (Reference R)
In house blood draw Deviation	Period-II	
	(b)(6) (2.00 hr)	--
Sample size	The sample size was changed from 24 subjects to 20 subjects as per sponsor's request. Hence the study was executed with 20 subjects.	

4.4.2.1.12 Summary of Standard Curve and QC Data for BE Sample Analyses

Bioequivalence Study No.: 060/18 Analyte Name (Sacubitril)										
Parameter	Standard Curve Samples									
	CC-01	CC-02	CC-03	CC-04	CC-05	CC-06	CC-07	CC-08	CC-09	CC-10
Concentration (ng/mL)	10.044	20.088	50.221	100.44	200.88	502.20	1201.4	2503.0	4501.8	5024.3
Inter day Precision (%CV)	1.1	2.7	3.3	2.1	2.0	2.0	1.6	1.6	1.9	2.0
Inter day Accuracy (%)	99.0	101.6	100.5	100.8	100.5	99.1	101.7	99.6	98.9	98.4
Linearity (Range of R ² Values)	0.9974 to 0.9998									

Linearity Range (ng/mL)	10.044 to 5024.3
Sensitivity/ LLOQ (ng/mL)	10.044

Bioequivalence Study No.: 060/18 Analyte Name (Sacubitril)				
Parameter	Quality Control Samples			
	HQC	MQC	AQC	LQC
Concentration (ng/mL)	3798.9	2002.0	1001.0	26.027
Inter day Precision (%CV)	2.1	1.9	2.0	2.7
Inter day Accuracy (%)	103.2	103.9	104.4	105.2

Bioequivalence Study No.: 060/18 Analyte Name (Valsartan)										
Parameter	Standard Curve Samples									
	CC-01	CC-02	CC-03	CC-04	CC-05	CC-06	CC-07	CC-08	CC-09	CC-10
Concentration (ng/mL)	14.074	28.147	70.368	140.74	281.47	703.68	1683.4	3507.2	6307.8	7040.0
Inter day Precision (%CV)	1.5	2.8	2.9	1.7	2.3	2.2	2.2	2.2	3.5	3.2
Inter day Accuracy (%)	98.1	102.1	102.9	101.4	102.2	100.2	102.0	99.3	96.0	95.9
Linearity (Range of R ² Values)	0.9962 to 0.9996									
Linearity Range (ng/mL)	14.074 to 7040.0									
Sensitivity/ LLOQ (ng/mL)	14.074									

Bioequivalence Study No.: 060/18 Analyte Name (Valsartan)				
Parameter	Quality Control Samples			
	HQC	MQC	AQC	LQC
Concentration (ng/mL)	5323.0	2805.2	1402.6	36.468
Inter day Precision (%CV)	2.8	2.9	2.8	3.2
Inter day Accuracy (%)	100.7	103.4	104.6	106.4

4.4.2.1.13 Reanalysis of Study Samples

Study No.: 060/18 (Sacubitril)

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
Pharmacokinetics repeats	00	00	0.00	0.00	00	00	0.00	0.00
Above Upper Limit of Quantification	32	49	4.01	5.83	32	49	4.01	5.83
Total	32	49	4.01	5.83	32	49	4.01	5.83

Note: Total number of test (T) samples analysed: 798
Total number of reference (R) samples analysed: 840

Study No.: 060/18 (Valsartan)								
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
Pharmacokinetics repeats	00	00	0.00	0.00	00	00	0.00	0.00
Inconsistent Internal Standard Response	00	02	0.00	0.23	00	02	0.00	0.23
Total	00	02	0.00	0.23	00	02	0.00	0.23

Note: Total number of test (T) samples analysed: 836
Total number of reference (R) samples analysed: 880

4.4.2.1.14 SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
(b)(4)		Reanalysis of study samples

4.4.2.2 Failed Pilot Fed BE Study No. 059/18

4.4.2.2.1 Submission Summary

Same as the failed pilot fasting BE study no. 060/18.

4.4.2.2.2 Study Information

Study Number	059/18
Study Title	An open label, balanced, randomized, two-treatment, two-period, two-sequence, single dose, crossover, oral bioequivalence study of Sacubitril and Valsartan tablets 97 mg/103 mg of Laurus Labs Limited, India comparing with ENTRESTOTM™ (sacubitril / valsartan) tablets 97mg/103 mg of Novartis Pharmaceuticals Corporation East Hanover,

	New Jersey 07936 in healthy, adult, human subjects under fed conditions			
Study Type	☒ In Vivo BE	☐ In Vitro BE	☐ Permeability	☐ Other (Specify)
Submission Location: Study Report	NA			
Validation Report	NA			
Bioanalytical Report	NA			
Clinical Site (Name, Address, Phone #, Fax #)	QPS Bioserve India Pvt. Limited, # 6-56/6/1A, Opp: IDPL Factory, Balanagar, Hyderabad-500 037, Telangana, India. Tel: +91-40-4377 0873 / 1875 Fax: +91-40-4377 0877			
Principal Clinical Investigator (Name, Email)	Dr. K.Babji babji.kalmanoor @qpsbioserve.com			
Analytical Site (Name, Address, Phone #, Fax #)	(b)(4)			
Principal Analytical Investigator (Name, Email)				
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)	(19/09/2018 to 13/10/2018) 25 days -20°C ± 10°C			
Long-Term Storage Stability (LTSS) Coverage (no. days @ temp °C)	147 days @ -20°C ± 10°C and -70° ± 15°C			
LTSS Data Location	NA			

4.4.2.2.3 Product Information

Same as the failed pilot fasting BE study no. 060/18.

4.4.2.2.4 Composition of Non-Standard Breakfast Meal Used in Fed Bioequivalence Study

Standard FDA Meal Used?	☐ Yes ☒ No				
If No, then meal components and composition is listed in the tables below					
Composition of Non-standard FDA Meal Used in Fed Bioequivalence Study (Study No. 059/18)					
Ingredients	Amount (g)	Energy (K Cal)	Protein (K Cal)	Fat (K Cal)	Carbohydrate (K Cal)
Bread toast with butter	34g of bread with 20 g of butter	234.01	11.24	148.05	74.72
Egg omelet	27	96.87	15.96	80.91	----

Fried chicken	72	171.77	77.72	94.05	----
Potato cutlet	110	281.55	9.60	136.35	135.6
Milk	240 mL	157.14	34.56	72.9	49.68
TOTAL		941.34	149.08	532.26	260.00
PERCENTAGE		100	15.84	56.54	27.62

4.4.2.2.5 Summary of Bioavailability Studies

Sacubitril

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range))	Mean Parameters +/-SD (%CV) for Sacubitril							Study Report Location
					C _{max} (ng/mL)	T _{max} (hr) Median (Range)	AUC _t (hr*ng/mL)	AUC _{inf} (hr*ng/mL)	t _{1/2} (hr)	k _{el} (hr ⁻¹)	AUC _{%Extrap}	
059/18	To assess the bioequivalence of Sacubitril and Valsartan tablets 97mg/103 mg of Laurus Labs Limited, India comparing with that of ENTRESTO™ (sacubitril / valsartan) tablets 97mg/103 mg of Novartis Pharmaceuticals Corporation East Hanover, New Jersey 07936 in healthy, adult, human subjects under fed conditions.	An open label, balanced, randomized, two-treatment, two-period, two-sequence, single dose, crossover oral bioequivalence study in healthy, adult, human subjects under fed conditions.	Test product (T): 01 tablet Sacubitril and Valsartan tablet 97mg/103 mg Administered orally Batch No. 15140-A-044	14 Healthy, adult, male, human subjects Age: 31.1 (23 – 41)	2410.0 ± 938.65 (38.948)	1.67 (0.33 - 5.00)	5287.788 ± 1415.547 (26.770)	5496.903 ± 1427.770 (25.974)	2.07 ± 3.31 (159.95)	0.5713 ± 0.2020 (35.3542)	3.213 ± 10.075 (313.599)	NA
					3111.2 ± 1345.0 (43.231)	2.00 (1.33 - 4.50)	5646.435 ± 1352.143 (23.947)	5696.034 ± 1355.010 (23.789)	1.67 ± 1.54 (92.69)	0.5606 ± 0.2104 (37.5403)	0.905 ± 1.017 (112.415)	
	To monitor adverse events and ensure the safety and tolerability of subjects		Reference product (R): 01 tablet ENTRESTO™ (sacubitril / valsartan) tablets 97mg/103 mg Administered orally Lot Number: FX000079									

Valsartan

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range))	Mean Parameters +/-SD (%CV) for Valsartan							Study Report Location
					C _{max} (ng/mL)	T _{max} (hr) Median (Range)	AUC _t (hr*ng/mL)	AUC _{inf} (hr*ng/mL)	t _{1/2} (hr)	k _{el} (hr ⁻¹)	AUC _{%Extrap}	
059/18	To assess the bioequivalence of Sacubitril and Valsartan tablets 97mg/103 mg of Laurus Labs Limited, India comparing with that of ENTRESTO™ (sacubitril / valsartan) tablets 97mg/103 mg of Novartis Pharmaceuticals Corporation East Hanover, New Jersey 07936 in healthy, adult, human subjects under fed conditions.	An open label, balanced, randomized, two-treatment, two-period, two-sequence, single dose, crossover oral bioequivalence study in healthy, adult, human subjects under fed conditions.	Test product (T): 01 tablet Sacubitril and Valsartan tablet 97mg/103 mg Administered orally Batch No. 15140-A-044	14 Healthy, adult, male, human subjects Age: 31.1 (23 – 41)	1721.0 ± 529.24 (30.752)	3.17 (2.00 - 10.00)	13718.120 ± 4611.922 (33.619)	14009.182 ± 4675.518 (33.375)	6.63 ± 3.00 (45.24)	0.1170 ± 0.0335 (28.6002)	2.168 ± 1.293 (59.626)	NA
					1850.0 ± 474.42 (25.644)	3.67 (2.00 - 4.50)	14318.079 ± 4965.996 (34.683)	14560.727 ± 4984.492 (34.232)	6.54 ± 3.07 (46.87)	0.1201 ± 0.0370 (30.8202)	1.795 ± 0.670 (37.337)	
	To monitor adverse events and ensure the safety and tolerability of subjects		Reference product (R): 01 tablet ENTRESTO™ (sacubitril / valsartan) tablets 97mg/103 mg Administered orally Lot Number: FX000079									

4.4.2.2.6 Statistical Summary of the Comparative Bioavailability Data

Reference Scaled Average Bioequivalence Approach Used					☐ Yes ☒ No	
If No, then complete Table 3A only If Yes, then complete Tables 3A and 3B						
Sacubitril and Valsartan tablets 97mg/103 mg (No of subjects completed= 14) Dose (1 X 97mg/103 mg)						
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fed Bioequivalence Study (Study No. 059/18) (Sacubitril)						
Parameter	Test	N	Reference	N	Ratio (%)	90% C.I.
AUC _t (hr*ng /mL)	5024.3659	14	5436.0285	14	92.43	87.53- 97.60
AUC _{inf} (hr*ng /mL)	5255.2521	14	5486.6160	14	95.78	87.83- 104.46
C _{max} (ng/ml)	2152.9224	14	2774.0681	14	77.61	66.03- 91.21
Fed Bioequivalence Study (Study No. 059/18) (Valsartan)						
Parameter	Test	N	Reference	N	Ratio (%)	90% C.I.
AUC _t (hr*ng /mL)	12813.6740	14	13300.0989	14	96.34	87.64 - 105.91
AUC _{inf} (hr*ng /mL)	13107.4899	14	13549.4819	14	96.74	88.12 - 106.20
C _{max} (ng/ml)	1610.3807	14	1765.7444	14	91.20	83.43 - 99.70

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	Outcome
LAUCT	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
LAUCI	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
LCMAX	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

4.4.2.2.7 Bioanalytical Method Validation

Same as the failed pilot fasting BE study no. 060/18.

4.4.2.2.8 Demographic Profile of Subjects Completing the Bioequivalence Study

Study No.: 059/18			
		Treatment Groups	
		Test Product (T) N=14	Reference Product (R) N=14
Age (years)	Mean ± SD	31.1 ± 5.8	31.1 ± 5.8
	Range	23.0 – 41.0	23.0 – 41.0
Age Groups	< 18	00	00
	18 – 40	13 (92.86%)	13 (92.86%)
	41 – 64	01 (7.14%)	01(7.14%)

	65 – 75	00	00
	> 75	00	00
Sex	Male	14 (100.0%)	14 (100.0%)
	Female	00	00
Race	Asian	14 (100.0%)	14 (100.0%)
	Black	00	00
	Caucasian	00	00
	Hispanic	00	00
	Other	00	00
BMI	Mean ± SD	22.3 ± 1.7	22.3 ± 1.7
	Range	19.7 – 24.8	19.7 – 24.8
Other Factors		NA	NA

4.4.2.2.9 Dropout Information

Study No. 059/18				
Subject No	Reason for dropout/replacement	Period	Replaced?	Replaced with
(b)(6)	Subject was withdrawn from the study as he did not turn up for period-II check-in. He was withdrawn at 23:00 hours on (b)(6)	II	No	NA
	Subject was withdrawn from the study as he did not turn up for period-II check-in. He was withdrawn at 23:02 hours on (b)(6)	II	No	NA

4.4.2.2.10 Incidence of Adverse Events in Individual Studies

Body System / Adverse	Reported Incidence by Treatment Groups		
	Fed Bioequivalence Study		
	Study No.: 059/18		
Event	Test (T)	Reference (R)	Post Study
There were no adverse events reported in this study			

4.4.2.2.11 Protocol Deviations

Study No.: 059/18		
Type	Subject #s (Test T)	Subject #s (Reference R)
There were no protocol deviations reported in this study		

4.4.2.2.12 Summary of Standard Curve and QC Data for BE Sample Analyses

Bioequivalence Study No.: 059/18 Analyte Name (Sacubitril)										
Parameter	Standard Curve Samples									
	CC-01	CC-02	CC-03	CC-04	CC-05	CC-06	CC-07	CC-08	CC-09	CC-10
Concentration (ng/mL)	10.044	20.088	50.221	100.44	200.88	502.20	1201.4	2503.0	4501.8	5024.3
Inter day Precision (%CV)	1.3	2.0	1.4	2.2	1.8	0.9	2.0	1.8	1.7	3.1
Inter day Accuracy (%)	99.4	100.7	100.8	101.5	100.1	99.0	102.3	99.8	98.9	97.7
Linearity (Range of R ² Values)	0.9990 to 0.9996									
Linearity Range (ng/mL)	10.044 to 5024.3									
Sensitivity/ LLOQ (ng/mL)	10.044									

Bioequivalence Study No.: 059/18 Analyte Name (Sacubitril)				
Parameter	Quality Control Samples			
	HQC	MQC	AQC	LQC
Concentration (ng/mL)	3798.9	2002.0	1001.0	26.027
Inter day Precision (%CV)	2.1	1.9	2.4	3.6
Inter day Accuracy (%)	101.8	103.4	104.2	104.5

Bioequivalence Study No.: 059/18 Analyte Name (Valsartan)										
Parameter	Standard Curve Samples									
	CC-01	CC-02	CC-03	CC-04	CC-05	CC-06	CC-07	CC-08	CC-09	CC-10
Concentration (ng/mL)	14.074	28.147	70.368	140.74	281.47	703.68	1683.4	3507.2	6307.8	7040.0
Inter day Precision (%CV)	1.6	3.2	2.3	2.9	2.4	1.0	2.5	2.1	1.1	2.0
Inter day Accuracy (%)	97.3	103.2	104.1	102.1	101.2	99.2	101.1	98.6	97.5	95.6
Linearity (Range of R ² Values)	0.9978 to 0.9988									
Linearity Range (ng/mL)	14.074 to 7040.0									
Sensitivity/ LLOQ	14.074									

(ng/mL)	

Bioequivalence Study No.: 059/18 Analyte Name (Valsartan)				
Parameter	Quality Control Samples			
	HQC	MQC	AQC	LQC
Concentration (ng/mL)	5323.0	2805.2	1402.6	36.468
Inter day Precision (%CV)	2.5	1.8	2.6	3.6
Inter day Accuracy (%)	100.6	103.2	104.4	104.8

4.4.2.2.13 Reanalysis of Study Samples

Study No.: 059/18 (Sacubitril)								
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
Pharmacokinetics repeats	00	00	0.00	0.00	00	00	0.00	0.00
Above Upper Limit of Quantification	00	01	0.00	0.31	00	01	0.00	0.31
Total	00	01	0.00	0.31	00	01	0.00	0.31

Note: Total number of test (T) samples analysed: 368
Total number of reference (R) samples analysed: 322

Study No.: 059/18 (Valsartan)								
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
Pharmacokinetics repeats	00	00	0.00	0.00	00	00	0.00	0.00
Total	00	00	0.00	0.00	00	00	0.00	0.00

Note: Total number of test (T) samples analysed: 384
Total number of reference (R) samples analysed: 336

4.4.2.2.14 SOP's Dealing with Bioanalytical Repeats of Study Samples

Same as the failed pilot fasting BE study no. 060/18.

4.4.2.3 Summary of In Vitro Dissolution Studies

Dissolution Conditions		(b)(4)									
Apparatus:		(b)(4)									
Speed of Rotation:		(b)(4)									
Medium:		(b)(4)									
Volume:		(b)(4)									
Temperature:		(b)(4)									
Firm's Proposed Specifications		(b)(4)									
Dissolution Testing Site (Name, Address)		Laurus Labs Limited, Research & Development Center, Plot No:DS1, IKP Knowledge Park, Genome Valley, Turkapally, Shameerpet, Hyderabad -500078, 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 or hours)			Study Report Location			
Study Report #. AR No: E-FDAR09 18/0021	01/09/20 18	Sacubitril and Valsartan Tablets B. No.: 15140-A-044 Manufacturing Date: Aug 2018.	97mg/103 mg Tablet	12	Sacubitril			Not Applicable			
					Mean	48	69		85	95	97
					Range	(b)(4)					
					%CV	17.1	15.0		12.5	7.3	1.9
Study Report #. AR No: E-FDAR09 18/0035	04/09/20 18	Entresto (Sacubitril and Valsartan) B. No.: FX000079 Expiry Date: July 2020.	97mg/103 mg Tablet	06	Valsartan			Not Applicable			
					Mean	48	69		86	96	98
					Range	(b)(4)					
					%CV	16.4	15.0		11.9	6.9	1.9
					Sacubitril						
					Mean	45	66		81	94	96
					Range	(b)(4)					
					%CV	12.5	4.1		4.3	2.6	0.5
					Valsartan						
					Mean	45	67		82	95	97
					Range	(b)(4)					
					%CV	12.2	4.1		4.3	2.5	0.6

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 or hours)					Study Report Location	
					10 min	15 min	20 min	30 min	45 min		
Study Report #. AR No: E-FDAR09 18/0414	21/09/20 18	Sacubitril and Valsartan Tablets B. No.: 15140-B-044 Manufacturing Date: Aug2018.	49mg/51 mg Tablet	06	Sacubitril					Not Applicable	
					Mean	66	87	96	97		97
					Range	(b)(4)					
					%CV	3.1	1.4	0.3	0.7		0.6
					Valsartan						
					Mean	67	88	98	98		98
Range	(b)(4)										
%CV	3.0	1.4	0.3	0.6	0.6						
Study Report #. AR No: E-FDAR05 18/0161	09/05/20 18	Entresto (Sacubitril and Valsartan) B. No.: FX000013 Expiry Date: Feb 2020.	49mg/51 mg Tablet	06	Sacubitril					Not Applicable	
					Mean	56	74	86	95		97
					Range	(b)(4)					
					%CV	4.8	3.9	3.2	2.4		1.6
					Valsartan						
					Mean	58	76	89	98		99
Range	(b)(4)										
%CV	4.5	3.7	3.1	2.2	1.6						
Study Report #. AR No: E-FDAR09 18/0415	28/09/20 18	Sacubitril and Valsartan Tablets B. No.: 15140-C-044 Manufacturing Date: Aug2018.	24mg/26 mg Tablet	06	Sacubitril					Not Applicable	
					Mean	69	90	96	96		96
					Range	(b)(4)					
					%CV	13.2	5.7	0.8	0.5		0.6
					Valsartan						
					Mean	71	92	97	97		97
Range	(b)(4)										
%CV	12.7	5.5	0.6	0.5	0.6						
Study Report	09/05/20 18	Entresto (Sacubitril and Valsartan) B. No.: FX000017	24mg/26 mg Tablet	06	Sacubitril					Not Applicable	
					Mean	65	89	98	99		99
					Range	(b)(4)					

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference - Expiration Date)	Dosage Strength & Form	No. of Dosage Units	%CV	Collection Times (minutes or hours)					Study Report Location
						10 min	15 min	20 min	30 min	45 min	
#. AR No: E- FDAR05 18/0160		Expiry Date: May 2020.				4.9	2.3	1.5	1.2	1.3	Not Applicable
						Valsartan					
						66	88	96	97	98	
						(b)(4)					
					%CV	4.7	2.2	1.4	1.3	1.2	

4.4.3 SAS Output

Study	SAS Data	SAS Code	SAS Stat	SAS Output/Table
Pivotal Fasting	 213676 SAC.xlsx	 ANDA 213676 SAC.sas	 SAC-STAT OUTPUT.doc	 SAC-ANALYSIS.doc
	 213676 VAL.xlsx	 ANDA 213676 VAL.sas	 VAL-STAT OUTPUT.doc	 VAL-ANALYSIS.doc
Pivotal Fed	 213676 SAC.xlsx	 ANDA 213676 SAC.sas	 SAC-STAT OUTPUT.doc	 SAC-ANALYSIS.doc
	 213676 VAL.xlsx	 ANDA 213676 VAL.sas	 VAL-STAT OUTPUT.doc	 VAL-ANALYSIS.doc

NOTE TO REGULATORY PROJECT MANAGER (RPM):

Currently, there is OSIS inspection(s) pending for the clinical site.

Per OGD Policy, as of 12/10/2019, there is a Policy Alert regarding the RLD ENTRESTO® (sacubitril and valsartan) Tablets stemming from Citizen Petition (CP) FDA-2019-P-1893. In addition, there is another policy alert regarding multiple drug products containing valsartan stemming from CP FDA-2019-P-2869. It is noted that the scope of this CP includes the current drug product, among other valsartan containing drug products.

No Approval Actions (AP/TA) can be taken prior to contacting Policy Lead and all disciplines can continue communications (CRL, IR/DRL). CC should contact Policy if related to CP.

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 213676
APPLICANT: Laurus Labs Limited
DRUG PRODUCT: Sacubitril and Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg

The Division of Bioequivalence I (DBI) has completed its assessment and has identified the following deficiencies:

Deficiency Related to Pre-Study Method Validation

1.

(b) (4)

Deficiency Related to Pivotal Fasting Bioequivalence (BE) Study (Study No. 662/18)

2. You reanalyzed 16 valsartan samples due to “Above Upper Limit of Quantification”. Following reanalysis using 2-fold dilution, it was found that several repeat samples from Subjects (b)(6) show plasma concentrations that are 24.2-66.2% lower than the highest calibration standard (10022 ng/mL). Please explain the significant

difference between the aforementioned repeat samples and ULOQ and its impact on dilution integrity.

Sincerely yours,

{ See appended electronic signature page }

Utpal Munshi, Ph.D.
Acting Director, Division of Bioequivalence I
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

5 OUTCOME

Completed Assignment for 213676 ID: 40625

Assessor: AbuZnait, Alaa

Date Completed:

Verifier: ,

Date Verified:

Division: Division of Bioequivalence

Description: Sacubitril and Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg, Original ANDA

Items:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Score</i>	<i>Subtotal</i>
40625	07/08/2019	BIO	ANDA Original [1]	1.00	1.00
40625	07/08/2019	Parallel	Fasting Study [1]	1.00	1.00
40625	07/08/2019	Parallel	Fasting Study (Additional Analyte) [0.25]	0.25	0.25
40625	07/08/2019	Parallel	Fed Study [1]	1.00	1.00
40625	07/08/2019	Parallel	Fed Study (Additional Analyte) [0.25]	0.25	0.25
40625	07/08/2019	Parallel	Pilot and Failed Full Extra Study for the Same Formulation as the Proposed Formulation (as defined in Guidance) [0.25]	0.25	0.25
40625	07/08/2019	Parallel	Pilot and Failed Full Extra Study for the Same Formulation as the Proposed Formulation (as defined in Guidance) [0.25]	0.25	0.25
40625	07/08/2019	Parallel	Dissolution-Based Waiver (IR) (For all waiver strengths) [0.25]	0.25	0.25
				Total:	4.25

DIVISION OF BIOEQUIVALENCE ASSESSMENT

BCS Waiver

ANDA No.	213676	
Drug Product Name	Sacubitril and Valsartan Tablets	
Strength(s)	24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg	
Applicant Name	Laurus Labs Limited	
Applicant Address	Second Floor, Serene Chambers, Road No.7, Banjara Hills Hyderabad, Telangana, India, 500034	
US Contact Name and US Mailing Address	Dr. Jose D. Gomes, Ph.D., President, PharmaQ, Inc. Waterview Plaza, 2001 Route 46, Suite 105 Parsippany, NJ 07054 jgomes@pharmaq.net	
US Contact Telephone Number	+(1)-973-402-5300	
US Contact Fax Number	+(1)-973-368-1145	
Original Submission and Amendment Date(s)	07/08/2019 (New/ANDA)	
Submission Date(s) of Amendment(s) Under Assessment	01/16/2020 (Bioequivalence/Response to Discipline Review Letter)	
Primary Assessor	Alaa H. Abuznait, Ph.D.	
Secondary Assessor	Dapeng Cui, Ph.D.	
Tertiary Assessor	N/A	
Study Number(s)	662/18	663/18
Study Type(s)	Fasting (Pivotal)	Fed (Pivotal)
Strength(s)	97 mg/103 mg	97 mg/103 mg
Clinical Site	QPS Bioserve India Pvt. Limited	
Clinical Site Address	# 6-56/6/1A, Opp: IDPL Factory, Balanagar, Hyderabad-500 037, Telangana, India	
Analytical Site	(b) (4)	
Analytical Site Address		
Study Number(s)	060/18	059/18
Study Type(s)	Fasting (Pilot, Failed)	Fed (Pilot, Failed)
Strength(s)	97 mg/103 mg	97 mg/103 mg
Clinical Site	QPS Bioserve India Pvt. Limited	

Clinical Site Address	Same as the pivotal BE studies	
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 ☐ N/A (Waiver/Deem Bioequivalent) ¹	<u>Post October 1, 2014 ANDAs</u> ☐ To Be Determined by OSIS ☐ Pending For Cause Inspection ☒ Complete ☐ N/A (Waiver/Deem Bioequivalent) ¹
Waiver/Deem Bioequivalent	☐ Granted ☐ Tentatively granted ☒ Not granted ☐ N/A	
QC Dissolution	☐ Pending ☒ Adequate ² ☐ Inadequate	
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	Bioanalytical and OSIS Deficiencies	
Justification for Major Designation	The bioequivalence deficiency(ies) has/have been classified as MAJOR because the deficiency pertain to insufficient validation data (i.e., insufficient long-term storage stability of valsartan and sacubitril in the pivotal fasting and fed BE studies) as noted in Appendix A, Section B.1.d of the Guidance for Industry, ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). The assessment of the response will require, in FDA’s judgment, a substantial expenditure of FDA resources. The bioequivalence deficiency(ies) has/have been classified as MAJOR because the deficiency pertain to information needed to address the impact of significant Office of Study Integrity Surveillance (OSIS) inspectional or assessment findings (i.e., failure to read serology results within the timeframes specified by the HIV, HCV, and HBsAg diagnostic test kits) as noted in Appendix A, Section B.1.k of the Guidance for Industry, ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). The assessment of the response will require, in FDA’s judgment, a substantial expenditure of FDA resources.	
Overall Assessment Result	☐ Adequate ☒ Inadequate	

¹ Requests submitted under 21 CFR 320.22(d)(2) or 320.24(b)(6).

² GDRP: ANDA-213676-ORIG-1, Biopharmaceutics Review, A213676 Biopharm R01-AQ.docx, 2/28/2020.

Product Specific Guidance (PSG) Referenced in Assessment	☒ Recommended/Latest Revision Date: April 2016³ RLD Number: NDA 207620 ☐ N/A (no PSG available at time of assessment)		
Revised/New Draft Guidance Generated as Part of Current Assessment	☐ YES ☒ NO		
Bioequivalence study tracking/supporting document #	Study/Test Type	Strength	Assessment Result
1, 6	Pivotal Fasting	97 mg/103 mg	☐ Adequate ☒ Inadequate
1, 6	Pivotal Fed	97 mg/103 mg	☐ Adequate ☒ Inadequate
1	Failed Pilot Fasting	97 mg/103 mg	For Information Purposes Only
1	Failed Pilot Fed	97 mg/103 mg	For Information Purposes Only
1, 6	Waiver	24 mg/26 mg, 49 mg/51 mg	☐ Adequate ☒ Inadequate

N/A = Not Available.

1 EXECUTIVE SUMMARY

This is an assessment of the amendment dated 1/16/2020 (Supporting Document 6).

The original application submitted on 7/8/2019 contained the results of pivotal fasting and fed bioequivalence (BE) studies comparing a test product, Laurus Labs Limited's Sacubitril and Valsartan Tablets, 97 mg/103 mg, to the corresponding reference standard (RS) product, Novartis Pharmaceuticals Corp's ENTRESTO[®] (sacubitril and valsartan) Tablets, 97 mg/103 mg (NDA 207620, approved on 7/7/2015⁴).

In the original BE assessment dated 1/14/2020⁵, the applicant's pivotal fasting and fed BE studies were found inadequate due to bioanalytical and method validation related deficiencies. In the current amendment dated 1/16/2020, the applicant's response to bioanalytical deficiency was found adequate while the response to method validation deficiency is inadequate because the long-term storage stability (LTSS) data for valsartan and sacubitril in the presence of active metabolite LBQ657 do not cover the sample storage duration in the pivotal fasting and fed BE studies.

³ Product-Specific Guidance on Sacubitril and Valsartan Tablets (Recommended Apr 2016), https://www.accessdata.fda.gov/drugsatfda_docs/psg/Sacubitril:%20Valsartan_oral%20tablet_RLD%20207620_RC04-16.pdf, accessed 3/31/2020.

⁴ Electronic Orange Book, https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=207620, accessed 3/31/2020.

⁵ GDRP: ANDA-213676-ORIG-1, Bioequivalence Review, A213676N000DB-Review01-07082019.docx, 1/14/2020.

At the time of the original BE assessment dated 1/14/2020⁵, the Office of Study Integrity and Surveillance (OSIS) inspection of the clinical BE site QPS Bioserve India Pvt., Ltd. [# 6-56/6/1A, Opp: IDPL Factory, Balanagar, Hyderabad-500 037, Telangana, India] was pending. The OSIS inspection of the clinical BE site for multiple ANDAs (i.e. ANDAs (b)(4)) was completed between September 16-20, 2019 with OSIS inspection outcome of voluntary action indicated (VAI) and Form 483 was issued⁶. The current BE assessor evaluated the findings reported in the OSIS Establishment Inspection Report (EIR) for the clinical BE site and determined that the OSIS Observation #1 and Discussion Item #1 do not impact the outcome of the pivotal fasting and fed BE studies in the current ANDA. However, the applicant will be asked to address the impact of Discussion Item #2 related to the delay in reading the results of serology testing kits on the outcomes of the pivotal fasting and fed BE studies submitted in the current ANDA. The OSIS inspection status for the current ANDA is now complete for the clinical and analytical sites.

The application remains **inadequate**.

NOTE TO REGULATORY PROJECT MANAGER (RPM):

Per OGD Policy, as of 3/23/2020, there is a Policy Alert regarding the RLD ENTRESTO® (sacubitril and valsartan) Tablets stemming from Citizen Petition (CP) FDA-2019-P-1893. In addition, there is another policy alert regarding multiple drug products containing valsartan stemming from CP FDA-2019-P-2869. It is noted that the scope of this CP includes the current drug product, among other valsartan containing drug products.

No Approval Actions (AP/TA) can be taken prior to contacting Policy Lead and all disciplines can continue communications (CRL, IR/DRL). CC should contact Policy if related to CP.

⁶ GDRP: ANDA-213676-ORIG-1, Clinical PK/PD Sites, Site: QPS BIOSERVE INDIA PVT. LIMITED. The OSIS memo, which covers the clinical site QPS Bioserve India Pvt., Ltd. in the current ANDA, is uploaded in the following location: ANDA-213208-ORIG-1, Clinical PK/PD Sites, Site: QPS BIOSERVE INDIA PVT. LIMITED, EIR Review - QPS final.pdf, 12/17/2019.

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3 ASSESSMENT OF THE CURRENT AMENDMENT SUBMISSION

Deficiency Related to Pre-Study Method Validation

Deficiency #1:

You prepared calibration curve standards (CCs) and quality control (QC) samples during pre-study method validation by spiking K₂EDTA plasma with methanolic working solution containing valsartan and sacubitril. Per RLD labeling, following drug product administration, sacubitril is converted to the active metabolite LBQ657, which would also be found in the study plasma samples. As such, the composition of QC samples is not reflective of the study samples composition. Therefore, please provide method validation data evaluating the impact of LBQ657 on the analysis of valsartan and sacubitril. Also, please demonstrate the stability of valsartan and sacubitril in the presence of LBQ657.

Applicant's Response to Deficiency #1:

We acknowledge the Agency's comment.

As per the Agency's recommendation, the impact of Sacubitril active metabolite LBQ657 (Desethyl sacubitril) on the analysis of valsartan and sacubitril was evaluated by performing a partial method validation in presence of LBQ657. The stability of Valsartan and sacubitril was also demonstrated in presence of LBQ657 during the partial method validation.

During the partial method validation, the following experiments were performed for the Quantification of valsartan and sacubitril in presence of LBQ657 in K₂EDTA human plasma using the same existing validated LC-MS/MS method. The summary of validation parameters are mentioned below:

(b) (4)

(b)(4)

During the partial method validation, the calibration curve standards and quality control samples were prepared in screened K₂EDTA human plasma. Only the QC samples were spiked with LBQ657 along with sacubitril and valsartan which mimics with the subject samples to evaluate the impact assessment on the analysis of valsartan and sacubitril.

All the partial method validation experiments were meeting the acceptance criteria. As evident from the partial method validation experiment results, there was no impact observed in the quantification of valsartan and sacubitril in presence of LBQ657 using the existing validated method. Therefore, the analytical method used for the estimation of sacubitril and valsartan in unknown subject samples was found adequate.

The method validation addendum report is provided Section 5.3.1.4 (Fasting and Fed) with this submission.

Assessor's Comments on Applicant's Response to Deficiency #1:

- As discussed in the original BE assessment dated 1/14/2020⁵, and per RLD labeling⁷, the study plasma samples for the pivotal fasting and fed BE studies (Study Nos. 662/18 and 663/18, respectively) contain the active sacubitril metabolite LBQ657 in addition to the parent analytes, valsartan and sacubitril. However, during the method validation and sample analysis for valsartan and sacubitril, calibration curve standards (CCs) and quality control (QC) samples were prepared by spiking K₂EDTA plasma with methanolic working solution containing valsartan and sacubitril only, which is not reflective of the study samples composition. Therefore, the applicant was asked to provide method validation and stability data evaluating the impact of LBQ657 on the analysis and stability of valsartan and sacubitril.
- In the current amendment, in response to the above deficiency, the applicant conducted partial method validation evaluating the effect of LBQ657 on the analysis of valsartan and sacubitril (Method Validation Addendum-IV No. MVR0379 V00 Addendum-IV; Report Date: January 10, 2020). According to the method validation addendum report, the CCs and QCs contain valsartan and sacubitril, and QCs were also spiked with LBQ657. The concentration of LBQ657 added (10002 ng/mL) is close to the highest CC for sacubitril (11991 ng/mL). The assessor finds the composition of CCs and QCs for the analysis of valsartan and sacubitril acceptable.
- The applicant validated the analytical method for selectivity, sensitivity, precision, accuracy, linearity, dilution integrity, and stability (bench-top, whole blood, re-injection reproducibility, processed samples stability, freeze & thaw stability, and

⁷ Drugs@FDA: RLD Labeling: Search by Keyword "207620",
https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/207620s0131bl.pdf, accessed 3/31/2020.

long-term storage stability (LTSS)). Except for LTSS, the results of partial method validation met the acceptance criteria specified in the method validation addendum report.

- Regarding LTSS, the assessor notes that the applicant has established LTSS for valsartan and sacubitril in the presence of LBQ657 for 3 days only at $-20^{\circ}\text{C} \pm 10^{\circ}\text{C}$ & $-70^{\circ}\text{C} \pm 15^{\circ}\text{C}$, which does not cover the sample storage duration of 51 days and 50 days reported for the pivotal fasting and fed BE studies, respectively, at $-20^{\circ}\text{C} \pm 10^{\circ}\text{C}$ at the clinical and analytical sites. The applicant will be asked to provide LTSS of valsartan and sacubitril in the presence of LBQ657 that cover the duration of sample storage from the first day of sample collection to the last day of sample analysis in the pivotal fasting and fed BE studies.

The applicant's response to Deficiency #1 is **incomplete**.

Deficiency Related to Pivotal Fasting Bioequivalence (BE) Study (Study No. 662/18)

Deficiency #2:

You reassayed 16 valsartan samples due to "Above Upper Limit of Quantification". Following reanalysis using 2-fold dilution, it was found that several repeat samples from Subjects (b)(6) show plasma concentrations that are 24.2-66.2% lower than the highest calibration standard (10022 ng/mL). Please explain the significant difference between the aforementioned repeat samples and ULOQ and its impact on dilution integrity.

Applicant's Response to Deficiency #2:

We acknowledge the Agency's comment.

As per the in-house SOP No (b)(4) Bioanalytical Method Validation, dilution integrity experiment was performed for the dilutions 1/2nd and 1/5th during the method validation. The specified analytical method for quantification of Valsartan and Sacubitril was found to be accurate and precise for 1/2nd and 1/5th diluted samples and found to be Linear for dilution. The dilution integrity experiment results for the analyte Valsartan are tabulated below:

(b) (4)

(b) (4)

During the subject samples analysis of pivotal fasting BE Study (Study No: 662/18), 16 samples were identified to be repeated under UL code-value above upper limit of quantification for the analyte Valsartan. As per the in-house SOP No (b)(4) Reanalysis of study samples, all the 16 individual samples were re-assayed under code UL-value above upper limit of quantification in singlet by diluting with 1/2nd dilution factor and re-assayed along with the dilution QCs in a single batch under analytical Run No: AR037. The analytical run meets the run acceptance criteria for calibration standards, QC samples and dilution QCs. Hence the repeated results were accepted and reported for all the 16 samples as per the 'Reanalysis of study samples' SOP.

As the dilution integrity quality control samples are meeting the acceptance criteria in terms of precision and accuracy, hence there could not be any impact on the dilutions of the samples done in the study.

Assessor's Comments on Applicant's Response to Deficiency #2:

- As discussed in the original BE assessment dated 1/14/2020⁵, 16 valsartan samples were reassayed due to "Above Upper Limit of Quantification". The repeat concentrations were within 15% of the highest calibration standard (ULOQ, 10022 ng/mL) after correcting for dilution factor except for repeat samples from Subjects (b)(6), whose repeat samples values were 24.2-66.2% lower than the ULOQ.
- In the current amendment, the applicant did not provide a clear explanation for the reason the valsartan repeat samples from Subjects (b)(6) show significant difference in concentration compared to ULOQ after 2-fold dilution. The applicant showed that the dilution integrity using dilution QC with concentration twice that of ULOQ (DQC = 20043 ng/mL) was found to be linear, precise, and accurate.

The applicant also explained that the aforementioned repeat samples were reassayed as per SOP (b)(4) "Reanalysis of Study Samples", which states:

"Above Upper Limit of Quantification (UL)

Samples for which the concentration exceeds the concentration of the highest calibration curve standards are repeated in singlet under this category of above upper limit of quantification.

The sample and two aliquots (minimum) of DQC sample are diluted to the established dilution with a screened matrix and analyzed.

The dilution integrity is considered as qualified, if the %RE acceptance criteria ($\pm 15\%$ of the nominal concentration) for at least 50% of DQC sample(s). The repeated result is multiplied by the dilution factor and the resultant value is reported.

If more than 50% of DQC sample(s) fails, the UL samples are repeated, if sample volume allows. Diluted DQC sample is not considered for overall statistical evaluation of the quality control samples.”

Since the applicant’s reassy of these samples is in line with SOP, and the DQC analyzed along with the repeat samples met the acceptance criteria per SOP (all 4 DQCs in the repeat run #AR037 were within $\pm 15\%$ of the nominal concentration), the assessor will not pursue this issue further.

The applicant’s response to Deficiency #2 is **adequate**.

4 OSIS STATUS FOR THE CLINICAL BE SITE QPS BIOSERVE INDIA PVT., LTD.

- The OSIS inspection of the clinical BE site QPS Bioserve India Pvt., Ltd. [# 6-56/6/1A, Opp: IDPL Factory, Balanagar, Hyderabad-500 037, Telangana, India] for ANDAs (b)(4) was completed between September 16-20, 2019 with OSIS inspection outcome of VAI and Form 483 was issued⁶. It is noted that the OSIS inspection report has been previously assessed by the BE assessors of the parent ANDAs (b)(4). The pivotal fasting (662/18) and fed (663/18) BE studies of current ANDA 213676 were submitted but not audited by the OSIS inspection. The current BE assessor evaluated OSIS findings and address their impact on current ANDA below.

OSIS Form 483 Observation 1:

Failure to assure that foreign clinical research was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" and the laws and regulations of

(b)(4)

the country in which the research was conducted. Specifically, Informed consent documents lack a description of reasonably foreseeable risks or discomforts to the subject.

a. Protocol 694-18, Section 7.8 - Warnings and Precautions, states patients suffering from the following should not take Mucinex[®] except upon medical advice: asthma, bronchitis, chronic obstructive pulmonary disease (COPD), emphysema, smokers, cough, and porphyria. This information is not documented within the approved Informed Consent (26 July 2018) issued to 44 subjects who were enrolled and participated in this trial.

The informed consent also does not provide information stated within the protocol regarding:

b. Drug interactions (Section 7.7) - Guaifenesin may increase the rate of absorption of paracetamol. Guaifenesin may interfere with some diagnostic measurements (urinary 5-hydroxyindoleacetic acid or vanillylmandelic acid).

c. Contraindications (Section 7.6) - Guaifenesin is contraindicated in patients with known hypersensitivity to guaifenesin or any component of the formulation.

Firm's Response to OSIS Form 483 Observation 1:

(b)(4)

OSIS Reviewer's Evaluation of OSIS Form 483 Observation 1:

(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)

Overall, the BE study submitted in the current ANDA does not indicate any conduct issues and no data integrity deficiencies related to the clinical and analytical sites were identified by the assessor. The OSIS inspection status is complete and **inadequate**.

NOTE TO REGULATORY PROJECT MANAGER (RPM):

Per OGD Policy, as of 3/23/2020, there is a Policy Alert regarding the RLD ENTRESTO® (sacubitril and valsartan) Tablets stemming from Citizen Petition (CP) FDA-2019-P-1893. In addition, there is another policy alert regarding multiple drug products containing valsartan stemming from CP FDA-2019-P-2869. It is noted that the scope of this CP includes the current drug product, among other valsartan containing drug products.

No Approval Actions (AP/TA) can be taken prior to contacting Policy Lead and all disciplines can continue communications (CRL, IR/DRL). CC should contact Policy if related to CP.

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 213676
APPLICANT: Laurus Labs Limited
DRUG PRODUCT: Sacubitril and Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg

The Division of Bioequivalence I (DBI) has completed its assessment and has identified the following deficiencies:

Deficiency Related to Pre-Study Method Validation

1. In your amendment dated 1/16/2020, in response to Discipline Review Letter (DRL) dated 12/12/2019, you provided the results of method validation for long term storage stability (LTSS) for valsartan and sacubitril in the presence of sacubitril active metabolite LBQ657. However, you only established LTSS for 3 days, which does not cover the sample storage duration of 51 days and 50 days reported for the pivotal fasting (Study No. 662/18) and fed (Study No. 663/18) bioequivalence (BE) studies, respectively, at $-20^{\circ}\text{C} \pm 10^{\circ}\text{C}$. Therefore, please provide LTSS data of valsartan and sacubitril in the presence of LBQ657 that cover the duration of sample storage from the first day of sample collection to the last day of sample analysis in the pivotal fasting and fed BE studies.

Office of Study Integrity and Surveillance (OSIS) Inspectional Deficiency

2. During an inspection conducted by OSIS from September 16-20, 2019 for other applications at the clinical site QPS Bioserve India Pvt., Ltd. [# 6-56/6/1A, Opp: IDPL Factory, Balanagar, Hyderabad-500 037, Telangana, India], the following issue was observed:

(b) (4)

Sincerely yours,

{ See appended electronic signature page }

Utpal Munshi, Ph.D.
Acting Director, Division of Bioequivalence I
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

5 OUTCOME

Completed Assignment for 213676 ID: 41711

Assessor: AbuZnait, Alaa

Date Completed:

Verifier: ,

Date Verified:

Division: Division of Bioequivalence

Description: Sacubitril and Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg, ANDA Amendment

Items:

<i>D</i>	<i>etter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>S re</i>	<i>Subt al</i>
41711	1/16/2020	BIO	ANDA Amendment [1]	1	1
41711	1/16/2020	Parallel	Major Amendment (original or supplement) [1.5]	1.5	1.5
4	1/16/2	Para	OSIS Inspection Report: Review of Systemic Observations Identified by the Parent Reviewer (irrespective of the number of sites/parent reviews) [0.25]		1
				Total	3.5

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 213676

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS



ANDA 213676

**INFORMATION REQUEST
QUALITY**

Laurus Generics inc.
U.S. Agent for Laurus Labs Ltd.
400 Connell Drive
Suite 5200
Berkeley Heights, NJ 07922
Attention: Sharath Koripally
Senior Director RA, QA & PV

Dear Sharath Koripally:

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 also refer to your May 15, 2023 submission, containing complete response.

We are reviewing the Quality section of your submission and request the following additional information/clarification and/or have the following comments:

QUALITY

A. Manufacturing

Facility

1.

(b) (4)

We request a complete written response, no later than June 13, 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 June 13, 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 Helina Zenebe, 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 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.



Erin
Andrews

Digitally signed by Erin Andrews

Date: 6/08/2023 12:29:02PM

GUID: 52e7d3790000f03cf7ec38aacca759ed



ANDA 213676

AMENDMENT ACKNOWLEDGEMENT
Standard
Major

Laurus Generics Inc.
U.S. Agent for Laurus Labs Limited
400 Connell Drive, Suite 5200
Berkeley Heights, NJ 07922
Attention: Sharath Koripally,
Senior Director - RA, QA & PV

Dear Sharath Koripally:

This is in reference to your amendment received on May 15, 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 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 January 15, 2024. If this standard major amendment requires an inspection, the goal date for review of this standard major amendment is March 15, 2024. 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, contact Warren Simmons, Regulatory Project Manager, at (240) 402 - 6258.

Sincerely,

{See appended electronic signature page}

Warren Simmons, Pharm.D.
LT, U.S. Public Health Service
Senior Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration



Warren
Simmons

Digitally signed by Warren Simmons

Date: 5/16/2023 11:11:11AM

GUID: 5499af3100542628231496828244f008



ANDA 213676

COMPLETE RESPONSE

Laurus Generics Inc.
U.S. Agent for Laurus Labs Limited
400 Connell Drive, Suite 5200
Berkeley Heights, NJ 07922
Attention: Sharath Koripally
Senior Director - RA, QA & PV

Dear Sharath Koripally:

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 March 17, 2022 submission, which constituted a complete response to our February 24, 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

Drug Substance

1.	(b) (4)
2.	

Drug Product

The drug product deficiencies have been classified as MAJOR as noted in Appendix A Section A(2)(i) in the Guidance for Industry, *ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA* (July 2018) because the firm may need to develop a new analytical method for nitrosamine impurity in DP or the firm should validate the FDA’s method and provide data to demonstrate that the in-house method is equivalent to the FDA’s method. Upon receipt, in FDA’s judgement, the review of this information will require thorough evaluation and potentially affects other aspects of the application and the related conclusions.

The drug product contains Valsartan (b)(4)

(b)(4)

(b)(4)

FDA’s published methods can be accessed at:
<https://www.fda.gov/drugs/drugsafety/ucm613916.htm>

Please provide us complete validation data and batch analyses data to demonstrate that your validated analytical method can detect and quantitate nitrosamines including NDMA in your drug product.

POLICY

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 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.

MANUFACTURING/ BIOPHARMACEUTICS/ 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.

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>.

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 that your ANDA addresses all listed patents and exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the Electronic Orange Book are addressed and updated in your application. Also, ensure that your labeling aligns with your patent and exclusivity statements.

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**

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. 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 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 Warren Simmons, Regulatory Project Manager, Division of Project Management, at (240) 402 - 6258.

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 2022 (GDUFA III) (Public Law 115-52, Title III).



David
Eng

Digitally signed by David Eng
Date: 12/20/2022 12:39:40PM
GUID: 508da6f500027e5b56adea7b0786cab9



ANDA 213676

AMENDMENT ACKNOWLEDGEMENT
Standard
Minor

Laurus Generics Inc.
U.S. Agent for Laurus Labs Limited
400 Connell Drive, Suite 5200
Berkeley Heights, NJ 07922
Attention: Sharath Koripally
Senior Director - RA, QA & PV

Dear Sharath Koripally:

This is in reference to your amendment received on September 23, 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 December 22, 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 Warren Simmons, Regulatory Project Manager, at (240) 402 - 6258.

Sincerely,

{See appended electronic signature page}

Warren Simmons, Pharm.D.
LT, U.S. Public Health Service
Senior Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration



Warren
Simmons

Digitally signed by Warren Simmons

Date: 9/26/2022 10:26:24AM

GUID: 5499af3100542628231496828244f008



ANDA 213676

AMENDMENT ACKNOWLEDGEMENT
Standard
Major

Laurus Generics Inc.
U.S. Agent for Laurus Labs Limited
400 Connell Drive, Suite 5200
Berkeley Heights, NJ 07922
Attention: Sharath Koripally
Senior Director - RA, QA & PV

Dear Sharath Koripally:

This is in reference to your amendment received on March 17, 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 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 November 16, 2022. If this standard major amendment requires an inspection, the goal date for review of this standard major amendment is January 16, 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 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 Warren Simmons, Regulatory Project Manager, at (240) 402 - 6258.

Sincerely,

{See appended electronic signature page}

Warren Simmons, Pharm.D.
LT, U.S. Public Health Service
Senior Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration



Warren
Simmons

Digitally signed by Warren Simmons

Date: 3/18/2022 04:51:27PM

GUID: 5499af3100542628231496828244f008



ANDA 213676

COMPLETE RESPONSE

Laurus Generics Inc.
U.S. Agent for Laurus Labs Limited
400 Connell Drive, Suite 5200
Berkeley Heights, NJ 07922
Attention: Sharath Koripally
Senior Director - Regulatory Affairs, QA & PV

Dear Sharath Koripally:

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 November 26, 2021 submission, which constituted a complete response to our October 4, 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

Drug Product

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.

(b) (4)

LABELING

1. GENERAL COMMENTS

a.

b.

(b)(4)

2. PRESCRIBING INFORMATION

a. HIGHLIGHTS

i. RECENT MAJOR CHANGES

(b)(4)

ii. INDICATIONS AND USAGE

(b)(4)

b. PRESCRIBING INFORMATION, INDICATIONS AND USAGE, Revise Section 1.1 Adult Heart Failure as follows:

(b)(4)

Left ventricular ejection fraction (LVEF) is a variable measure, so use clinical judgment in deciding whom to treat [see Clinical Studies (14.1)].

[We note the second paragraph is considered general clinical practice information.]

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.

DRUG SUBSTANCE/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 PRODUCT/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, 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 Warren Simmons, Regulatory Project Manager, Division of Project Management, at (240) 402 - 6258.

Sincerely yours,

{See appended electronic signature page}

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).



Denise
Toyer McKan

Digitally signed by Denise Toyer McKan
Date: 2/23/2022 02:35:39PM
GUID: 5277df670008860f7e1231f730a8684c



ANDA 213676

**AMENDMENT ACKNOWLEDGEMENT
Standard
Minor**

Laurus Generics Inc.
U.S. Agent for Laurus Labs Limited
400 Connell Drive, Suite 5200
Berkeley Heights, NJ 07922
Attention: Sharath Koripally
Senior Director - RA, QA & PV

Dear Sharath Koripally:

This is in reference to your amendment received on November 26, 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 February 25, 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 Warren Simmons, Regulatory Project Manager, at (240) 402 - 6258.

Sincerely,

{See appended electronic signature page}

Warren Simmons, Pharm.D.
LT, U.S. Public Health Service
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration



Warren
Simmons

Digitally signed by Warren Simmons

Date: 11/29/2021 11:02:39AM

GUID: 5499af3100542628231496828244f008



ANDA 213676

COMPLETE RESPONSE

Laurus Generics Inc.
U.S. Agent for Laurus Labs Limited
400 Connell Drive, Suite 5200
Berkeley Heights, NJ 07922
Attention: Sharath Koripally
Senior Director - RA, QA & PV

Dear Sharath Koripally:

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 May 3, 2021 submission, which constituted a complete response to our February 22, 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.

LABELING

1. GENERAL COMMENTS

(b) (4)

2. CARTON LABELING

Unit-dose 100s (10x10)- To be consistent with the RLD's cartons, consider adding "For Institutional Use Only." statement.

3. PRESCRIBING INFORMATION

- a. HIGHLIGHTS, INDICATIONS AND USAGE- Revise to read the same as the RLD.

i. (b) (4)
ii. (b) (4)

- b. HIGHLIGHTS, RECENT MAJOR CHANGES- Revise to read the same as the RLD labeling.

- c. INDICATIONS AND USAGE- Revise to read the same as the RLD or provide a comment why you feel this information should not be included.

i. (b) (4)
ii. (b) (4)

- d. Clinical Trials, Section 6

e. (b) (4)

(b)(4)

4. PATIENT INFORMATION LEAFLET

(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 (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.

**DRUG SUBSTANCE/DRUG PRODUCT/BIOPHARMACEUTICS/MANUFACTURING/
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
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, 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 Warren Simmons, Regulatory Project Manager, Division of Project Management, at (240) 402 - 6258.

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).



Aaron
Sigler

Digitally signed by Aaron Sigler
Date: 10/04/2021 02:18:56PM
GUID: 508da6fa0002827f1a9f2526d1b2cc69



ANDA 213676

AMENDMENT ACKNOWLEDGEMENT
Standard
Minor

PharmaQ, Inc.
U.S. Agent for Laurus Labs Limited
Waterview Plaza
2001 Route 46, Suite 105
Parsippany, NJ 07054
Attention: Jose D. Gomes, Ph.D.
President

Dear Sir:

This is in reference to an amendment to the Drug Master File (DMF) #033647 received on July 9, 2021, which is referenced in your abbreviated new drug application (ANDA) 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 October 8, 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 Warren Simmons, Regulatory Project Manager, at (240) 402 - 6258.

Sincerely,

{See appended electronic signature page}

Warren Simmons, Pharm.D.
LT, U.S. Public Health Service
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration



Warren
Simmons

Digitally signed by Warren Simmons

Date: 7/28/2021 03:30:52PM

GUID: 5499af3100542628231496828244f008



ANDA 213676

AMENDMENT ACKNOWLEDGEMENT
Standard
Minor

PharmaQ, Inc.
U.S. Agent for Laurus Labs Limited
Waterview Plaza
2001 Route 46, Suite 105
Parsippany, NJ 07054
Attention: Jose D. Gomes, Ph.D.
President

Dear Sir:

This is in reference to your amendment received on May 3, 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 August 2, 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 Warren Simmons, Regulatory Project Manager, at (240) 402 - 6258.

Sincerely,

{See appended electronic signature page}

Warren Simmons, Pharm.D.
LT, U.S. Public Health Service
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration



Warren
Simmons

Digitally signed by Warren Simmons

Date: 5/06/2021 12:25:55PM

GUID: 5499af3100542628231496828244f008



ANDA 213676

COMPLETE RESPONSE

PharmaQ, Inc.
U.S. Agent for Laurus Labs Limited
Waterview Plaza
2001 Route 46, Suite 105
Parsippany, NJ 07054
Attention: Dr. Jose D. Gomes, Ph.D.
President

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 July 1, 2020 submission, which constituted a complete response to our May 4, 2020 action 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.
2. (b) (4)

Drug Product

3.

(b)(4)

**PROCESS/BIOPHARMACEUTICS/FACILITY INSPECTION/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.

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>.

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 that your ANDA addresses all listed patents and exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the Electronic Orange Book are addressed and updated in your application. Also, ensure that your labeling aligns with your patent and exclusivity statements.

OTHER

The resubmission to this CR letter will be considered to represent a **MINOR AMENDMENT**, given that the deficiencies have been classified as **MINOR**. 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**

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 Warren Simmons, Regulatory Project Manager, Division of Project Management, at (240) 402 - 6258.

Sincerely yours,

{See appended electronic signature page}

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).



Denise
Toyer McKan

Digitally signed by Denise Toyer McKan
Date: 2/22/2021 04:27:23PM
GUID: 5277df670008860f7e1231f730a8684c



ANDA 213676

AMENDMENT ACKNOWLEDGEMENT
Standard
Major

PharmaQ, Inc.
U.S. Agent for Laurus Labs Limited
Waterview Plaza
2001 Route 46, Suite 105
Parsippany, NJ 07054
Attention: Jose Gomes
President

Dear Sir:

This is in reference to your amendment received on July 1, 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 February 28, 2021. If this standard major amendment requires an inspection, the goal date for review of this standard major amendment is April 30, 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 Warren Simmons, Regulatory Project Manager, at (240) 402 - 6258.

Sincerely,

{See appended electronic signature page}

Warren Simmons
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration



Chad
Snuggerud

Digitally signed by Chad Snuggerud

Date: 7/07/2020 09:32:04AM

GUID: 5407887b000a1c5c5a12a8c6e61df812



ANDA 213676

COMPLETE RESPONSE

PharmaQ, Inc.
U.S. Agent for Laurus Labs Limited
Waterview Plaza
2001 Route 46, Suite 105
Parsippany, NJ 07054
Attention: Jose Gomes, Ph.D.
President

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

(b) (4)

1. (b) (4)

2.

(b)(4)

Drug Product

3.

4.

5.

(b)(4)

6.

Facility Inspection

(b)(4)

7.

(b)(4)

BIOEQUIVALENCE

The Bioequivalence deficiencies have been classified as MAJOR because the deficiencies pertain to insufficient validation data (i.e., insufficient long-term storage

stability of valsartan and sacubitril in the pivotal fasting and fed BE studies) and In addition, information is needed to address the impact of significant Office of Study Integrity Surveillance (OSIS) inspectional or assessment findings (i.e., failure to read serology results within the timeframes specified by the HIV, HCV, and HBsAg diagnostic test kits) as noted in Appendix A, Sections B(1)(d) and B(1)(k) of the Guidance for Industry, ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). The assessment of the response will require, in FDA's judgment, a substantial expenditure of FDA resources.

Pre-Study Method Validation

1. In your amendment dated January 16, 2020, in response to Discipline Review Letter (DRL) dated December 12, 2019, you provided the results of method validation for long term storage stability (LTSS) for valsartan and sacubitril in the presence of sacubitril active metabolite LBQ657. However, you only established LTSS for 3 days, which does not cover the sample storage duration of 51 days and 50 days reported for the pivotal fasting (Study No. 662/18) and fed (Study No. 663/18) bioequivalence (BE) studies, respectively, at $-20^{\circ}\text{C} \pm 10^{\circ}\text{C}$. Therefore, please provide LTSS data of valsartan and sacubitril in the presence of LBQ657 that cover the duration of sample storage from the first day of sample collection to the last day of sample analysis in the pivotal fasting and fed BE studies.

Office of Study Integrity and Surveillance (OSIS) Inspection

2.

(b) (4)

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>.

PROCESS/BIOPHARMACEUTICS/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.

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.

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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/FACILITY INSPECTION/
BIOEQUIVALENCE**

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 Warren Simmons, Regulatory Project Manager, Division of Project Management, at (240) 402 - 6258.

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: 5/04/2020 01:47:38PM

GUID: 529372550000cc96a0a98e57d06862e5



ANDA 213676

INFORMATION REQUEST

Laurus Labs Limited
U.S. Agent for Laurus Labs Limited
2001 Route 46, Suite 105
Parsippany, NJ 07054-1315
Attention: Jose D. Gomes

Dear Sir:

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. Biopharm

(b) (4)

We request a prompt written response, no later than 3/1/20 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.

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 Kevin Ninan, Regulatory Business Process Manager, at Kevin.Ninan@fda.hhs.gov or 240-402-8732.

Sincerely,

{See appended electronic signature page}

Kevin Ninan
Regulatory Business Process Manager
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
U.S. Food and Drug Administration



Kevin
Ninan

Digitally signed by Kevin Ninan
Date: 2/20/2020 03:39:35PM
GUID: 5130b7c1000123364dc4c595d0d94f5f



GENERAL ADVICE

Laurus Labs Ltd
Attn: Jose D. Gomes
President
Email: jgomes@pharmaq.net

Dear Jose D. Gomes:

This letter is to update applicants with an approved or pending application for an angiotensin II receptor blocker (ARB) drug product (DP), as well as holders of related drug master files (DMFs), of FDA's current expectations of specification limits (b)(4)

(b)(4)

(b)(4)

(b) (4)

If you have any questions, call Rey Cantave, Regulatory Project Manager, at 240-402-4035.

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 12:38:19PM

GUID: 508da70600028a7aad41a1cc455d8261

Comments: singed off



ANDA 213676

**DISCIPLINE REVIEW LETTER
QUALITY**

PharmaQ, Inc.
U.S. Agent for Laurus Labs Limited
Waterview Plaza, 2001 Route 46,
Suite 105
Parsippany, NJ 07054
Attention: Jose D. Gomes
President

Dear Jose D. Gomes:

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.

The following possible deficiencies have been identified by the Office of Pharmaceutical Quality:

A. Drug Substance

1.

2.

3.

4.

(b) (4)

B. Drug Product

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)

D. Biopharmaceutics

1. Based on the provided information and data, the proposed dissolution method (USP II at 50 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 (b)(4) dissolution acceptance criteria and therefore the proposed acceptance criterion is not acceptable. Implement the following acceptance criteria for your proposed product, Sacubitril and Valsartan Tablets:

Sacubitril and Valsartan Tablets, 24 mg/26 mg strength

(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.

2.

(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 February 6, 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

¹ GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (available at: <https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf>).

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 Kevin Ninan, Regulatory Business Process Manager, at Kevin.Ninan@fda.hhs.gov or 240-402-8732.

Sincerely,

{See appended electronic signature page}

Kevin Ninan, PharmD
Regulatory Business Process Manager

Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
U.S. Food and Drug Administration



Kevin
Ninan

Digitally signed by Kevin Ninan
Date: 1/03/2020 11:05:20AM
GUID: 5130b7c1000123364dc4c595d0d94f5f

ANDA 213676

**DISCIPLINE REVIEW LETTER
BIOEQUIVALENCE**

PharmaQ, Inc.
U.S. Agent for Laurus Labs Limited
Waterview Plaza, 2001 Route 46, Suite 105
Parsippany, NJ 07054
Attention: Jose D. Gomes
President

Dear Jose D. Gomes:

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.

The following possible deficiencies have been identified by BIOEQUIVALENCE:

Deficiency Related to Pre-Study Method Validation

1. You prepared calibration curve standards (CCs) and quality control (QC) samples during pre-study method validation by spiking K₂EDTA plasma with methanolic working solution containing valsartan and sacubitril. Per RLD labeling, following drug product administration, sacubitril is converted to the active metabolite LBQ657, which would also be found in the study plasma samples. As such, the composition of QC samples is not reflective of the study samples composition. Therefore, please provide method validation data evaluating the impact of LBQ657 on the analysis of valsartan and sacubitril. Also, please demonstrate the stability of valsartan and sacubitril in the presence of LBQ657.

Deficiency Related to Pivotal Fasting Bioequivalence (BE) Study (Study No. 662/18)

2. You reassayed 16 valsartan samples due to "Above Upper Limit of Quantification". Following reanalysis using 2-fold dilution, it was found that several repeat samples from Subjects (b)(6) show plasma concentrations that are 24.2-66.2% lower than the highest calibration standard (10022 ng/mL). Please explain the significant difference between the aforementioned repeat samples and ULOQ and its impact on dilution integrity.

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
BIOEQUIVALENCE**

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

¹ GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (available at: <https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf>).

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 Jenny Choi, Bioequivalence Project Manager, at jenny.choi@fda.hhs.gov or (240) 402 - 3433.

Sincerely,

{See appended electronic signature page}

Jenny Choi, Pharm.D.
Project Manager
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research



Jenny
Choi

Digitally signed by Jenny Choi

Date: 12/12/2019 06:39:09PM

GUID: 555e0102000a87a04c594eb0537bc868



ANDA 213676

**DISCIPLINE REVIEW LETTER
LABELING**

PharmaQ, Inc
U.S. Agent For: Laurus Labs Limited
Waterview Plaza
2001 Route 46, Suite 105
Parsippany, NJ 07054
Attention: Jose Gomes
President,

Dear Dr. Gomes:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on July 08, 2019, 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.

The following possible deficiencies have been identified by LABELING:
Labeling Deficiencies determined on October 1, 2019, based on your submission received July 8, 2019:

1. CONTAINERS 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg in bottles of 30s, 60s, and 180s.
 - a. Relocate the net quantity statement to the bottom portion of label or very top (on same line as NDC statement) further away from the declaration of strength statement to prevent medication errors.
 - b. Insert a hyphen in "film-coated" and revise the "Each film-coated tablet..." statements so that the amount of active ingredient is consistent with the Description section in the insert. (b)(4)
2. UNIT DOSE BLISTERS and CARTONS, 100s (10 x10 unit dose blisters)
 - a. Revise "Each film-coated tablet contains..." statements so that the amount of active is consistent with the insert, description section. (b)(4)
(b)(4)
 - b. (b)(4)

3. PRESCRIBING INFORMATION

a. Revise your labeling to be in accordance with the labeling for the reference listed drug (RLD), Entresto (sacubitril and valsartan) tablets, NDA 207620/S-013, approved 10/1/2019. Labeling is posted at Drugs@FDA website.

b. (b)(4)

c. In addition to the above changes, please note the following minor editorial change request: HIGHLIGHTS, title line, replace "TABLETS" with lower case letters "tablets". See the RLD labeling for guidance.

d. (b)(4)

4. PATIENT LEAFLET- See comments under prescribing information.

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 Orange Book are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

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 November 08, 2019. 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 LABELING

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 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.

¹ GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (available at: <https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf>).

If you have any questions, please contact Juliette Larmie-Gyamfi, Labeling Project Manager, at Juliette.Larmie-Gyamfi@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Juliette Larmie-Gyamfi, Pharm.D.
Labeling Project Manager
Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research



Juliette
Larmie-Gyamfi

Digitally signed by Juliette Larmie-Gyamfi
Date: 10/25/2019 02:44:20PM
GUID: 5508755d000926ebceca6d5de2d276c5

ANDA 213676

INFORMATION REQUEST

Laurus Labs Limited
U.S. Agent for Laurus Labs Limited
2001 Route 46, Suite 105
Parsippany, NJ 07054-1315
Attention: Jose D. Gomes

Dear Sir:

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. Facility

(b) (4)

We request a prompt written response, no later than 9/15/19 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.

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/FACILITY

If you have any questions, please contact Kevin Ninan, Regulatory Business Process Manager, at kevin.ninan@fda.hhs.gov or 240-402-8732.

Sincerely,

{See appended electronic signature page}

Kevin Ninan, Pharm D
Regulatory Business Process Manager
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
U.S. Food and Drug Administration



Kevin
Ninan

Digitally signed by Kevin Ninan
Date: 9/09/2019 02:44:34PM
GUID: 5130b7c1000123364dc4c595d0d94f5f



ANDA 213676

**PARAGRAPH IV ACKNOWLEDGEMENT
ANDA RECEIPT**

PharmaQ, Inc.
U.S. Agent for Laurus Labs Limited
Waterview Plaza, 2001 Route 46, Suite 105
Parsippany, NJ 07054
Attention: Jose D. Gomes

Dear Jose D. Gomes:

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 (FD&C Act). The Food and Drug Administration (FDA or the Agency) has made a threshold determination that this ANDA is substantially complete. This ANDA is received for review.

NAME OF DRUG: Sacubitril and Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg

DATE OF APPLICATION: July 7, 2019

DATE (RECEIVED) ACCEPTABLE FOR REVIEW: July 8, 2019

You have filed a paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and section 505(j)(2)(A)(vii)(IV) of the FD&C Act. Please note that you must comply with the notice requirements, as outlined below.

NOTICE OF CERTIFICATION

You must send notice of your paragraph IV certification on or after the date you receive this paragraph IV acknowledgment letter from FDA, but not later than 20 days after the date of the postmark, as defined in 21 CFR 314.3, on this paragraph IV acknowledgment letter.

Send notice by U.S. registered or certified mail, return receipt requested, or by a designated delivery service (as described in 21 CFR 314.95(g)) to each of the following persons:

- (1) Each owner of the patent(s) or the representative(s) designated by the owner to receive the notice.
- (2) The holder of the approved new drug application (NDA) under section 505(b) of the FD&C Act for the listed drug that is claimed by the patent and for which the applicant

is seeking approval, or, if the NDA holder does not reside or maintain a place of business within the United States, the NDA holder's attorney, agent, or other authorized official.

An applicant may send notice by an alternate method only if FDA has agreed in advance that the method will provide an acceptable form of documentation.

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the FD&C Act, and the notice must include, but is not limited to, the following information:

- (1) A statement that FDA has received an ANDA submitted by the applicant containing any required bioavailability or bioequivalence data or information.
- (2) The ANDA number.
- (3) A statement that the applicant has received the paragraph IV acknowledgment letter for the ANDA.
- (4) The established name, if any, as defined in section 502(e)(3) of the FD&C Act, of the proposed drug product.
- (5) The active ingredient, strength, and dosage form of the proposed drug product.
- (6) The patent number and expiration date of each listed patent for the reference listed drug alleged to be invalid, unenforceable, or not infringed.
- (7) A detailed statement of the factual and legal basis of the applicant's opinion that the patent is not valid, unenforceable, or will not be infringed. The applicant must include in the detailed statement:
 - a. For each claim of a patent alleged not to be infringed, a full and detailed explanation of why the claim is not infringed.
 - b. For each claim of a patent alleged to be invalid or unenforceable, a full and detailed explanation of the grounds supporting the allegation.
- (8) If the applicant alleges that the patent will not be infringed and the applicant seeks to preserve the option to later file a civil action for declaratory judgment in accordance with section 505(j)(5)(C) of the FD&C Act, then the notice must be accompanied by an offer of confidential access to the ANDA for the sole and limited purpose of evaluating possible infringement of the patent that is the subject of the paragraph IV certification.
- (9) If the applicant does not reside or have a place of business in the United States, the name and address of an agent in the United States authorized to accept service of process for the applicant.

See 21 CFR 314.95.

DOCUMENTATION OF TIMELY SENDING AND RECEIPT OF NOTICE

Within 30 days after the last date on which notice was received by a person described in 21 CFR 314.95(a), you must submit an amendment to this ANDA with the following:

- In accordance with 21 CFR 314.95(b)(3), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that the notice met the content requirements under 314.95(c). A copy of the notice itself need not be provided to the Agency.

- In accordance with 21 CFR 314.95(e), provide documentation that the notice was sent on a date that complies with the timeframe required by 314.95(b) or (d) and a dated printout of the entry for the reference listed drug in FDA's "Approved Drug Products With Therapeutic Equivalence Evaluations" that includes the patent that is the subject of the paragraph IV certification. FDA will accept, as adequate documentation of the date the notice was sent, a copy of the registered mail receipt, certified mail receipt, or receipt from a designated delivery service (as described in 314.95(g)). FDA will accept as adequate documentation of the date of receipt a return receipt, signature proof of delivery by a designated delivery service, or a letter acknowledging receipt by the person provided the notice. An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.
- A designation on the cover page of the submission should clearly state "PATENT AMENDMENT".

NOTIFICATION OF FILING OF LEGAL ACTION

You must submit an amendment to your ANDA within 14 days of the filing of any legal action filed within 45 days of receipt of the notice of paragraph IV certification by any recipient. See 21 CFR 314.107(f)(2). The notification to FDA of the legal action must include:

- (1) The ANDA number.
- (2) The name of the ANDA applicant.
- (3) The established name of the drug product or, if no established name exists, the name(s) of the active ingredient(s), the drug product's strength, and dosage form.
- (4) A statement that an action for patent infringement, identified by court, case number, and the patent number(s) of the patent(s) at issue in the action, has been filed in an appropriate court on a specified date.

If a legal action is not filed within 45 days of receipt of the notice of paragraph IV certification by any recipient, please submit an amendment to your ANDA immediately after the 45 day period elapses stating that no legal action was taken by each person provided notice.

NOTIFICATION OF COURT ACTIONS OR WRITTEN CONSENT TO APPROVAL

You must submit an amendment to your ANDA within 14 days of the date of entry by the court of an action described in the following list, the date of appeal or expiration of the time for appeal, or the date of written consent to approval, as applicable. See 21 CFR 314.107(e). The amendment must include, as applicable:

- (1) A copy of any judgment by the court (district court or mandate of the court of appeals) or settlement order or consent decree signed and entered by the court (district court or court of appeals) finding a patent described in 314.107(b)(3) invalid, unenforceable, or not infringed, or finding the patent valid and infringed.
- (2) Written notification of whether or not any action by the court has been appealed within the time permitted for an appeal.
- (3) A copy of any order entered by the court terminating the 30-month or 7½-year period as described in 314.107(b)(3)(i), (b)(3)(ii), (b)(3)(vii), or (b)(3)(viii).
- (4) A copy of any written consent to approval by the patent owner or exclusive patent licensee described in 314.107(b)(3)(vi).

- (5) A copy of any preliminary injunction described in 314.107(b)(3)(v) and a copy of any subsequent court order lifting the injunction.
- (6) A copy of any court order pursuant to 35 U.S.C. 271(e)(4)(A) ordering that an ANDA may be approved no earlier than the date specified (irrespective of whether the injunction relates to a patent described in 314.107(b)(3)).

If you have further questions, you may contact the Patent and Exclusivity Team at CDER-OGDPET@fda.hhs.gov.

This original ANDA is subject to the provisions of the Generic Drug User Fee Amendments of 2017 (GDUFA II). Your request for a priority review of this submission meets the criteria listed in section 505(j)(11)(A) of the FD&C Act or 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*. However, a Pre-Submission Facility Correspondence was not submitted or was found ineligible for further assessment. The GDUFA II goal date for review of this priority original ANDA is May 7, 2020.

A drug with a name recognized in the USP National Formulary (USP–NF) generally must comply with applicable compendial standards or the drug will be deemed adulterated, misbranded, or both. (See section 501(b) and 502(e)(3)(b) and (g) of the Federal Food, Drug, and Cosmetic Act (FD&C Act); also 21 CFR 299.5(a) and (b)). Such drugs must also comply with compendial standards for strength, quality, and purity, unless labeled to show all respects in which the drug differs or they will be deemed adulterated. (See section 501(b) of the FD&C Act and 21 CFR 299.5(c)). If the proposed specifications for your product do not conform with an applicable official USP monograph, you are advised to contact USP upon receipt of this Acknowledgement Letter to initiate a monograph revision through the USP Pending Monograph Process (PMP). Please note that initiation of the PMP does not mean that the proposed specifications will necessarily be approved by FDA; revisions to the USP monograph will be contingent upon FDA approval of the proposed specifications in this application.

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd.

Please identify any related communications with the ANDA number referenced above. If you have any questions, contact Warren Simmons, Regulatory Project Manager, at

warren.simmons@fda.hhs.gov¹ or (240) 402 - 6258. We also recommend that you sign up for Generic Drug e-mail updates,² which provide updates and information generally related to generic drug regulation.

Sincerely,

{See appended electronic signature page}

Julie Chung, Pharm.D.
Team Leader
Division of Filing Review
Office of Regulatory Operations
Office of Generic Drugs

¹ A secure email address is recommended for applicants to utilize when communicating with the Agency. If you have not already established a secure email with FDA, you may send a request for a secure email address to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications. Formal regulatory submissions must be submitted according to FDA regulations and current guidances.

² <https://updates.fda.gov/subscriptionmanagement>



Julie
Chung

Digitally signed by Julie Chung
Date: 8/30/2019 07:25:45AM
GUID: 594c33cb00138bbf8775806464b00ee5