

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
ANDA 213719

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

Sponsor: Zydus Pharmaceuticals (USA) Inc.

Approval Date: July 09, 2024

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APPLICATION NUMBER:

ANDA 213719

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APPLICATION NUMBER:
ANDA 213719

APPROVAL LETTER



ANDA 213719

ANDA APPROVAL

Zydus Pharmaceuticals (USA) Inc.
73-B, Route 31 North
Pennington, NJ 08534
Attention: Srinivas Gurram
Senior Vice President - Head of Regulatory Affairs and CQA Lead - Americas

Dear Srinivas Gurram:

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 May 9, 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 Corporation (Novartis).

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

<u>U.S. Patent Number</u>	<u>Expiration Date</u>
8,101,659 (the '659 patent)	July 15, 2025*
8,877,938 (the '938 patent)	November 27, 2027*
9,388,134 (the '134 patent)	May 8, 2027*
9,517,226 (the '226 patent)	August 22, 2033

U.S. Food & Drug Administration
Silver Spring, MD 20993
www.fda.gov

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 Zydus Pharmaceuticals (USA) Inc. (Zydus) 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 Zydus for infringement of the '659, '938 and '134 patents in the United States District Court for the District of Delaware [Novartis Pharmaceuticals Corporation v. Zydus Pharmaceuticals (USA) Inc., et al., Civil Action No. 19-02053]. You have also notified the Agency that this case was dismissed.

With respect to 180-day generic drug exclusivity, we note that Zydus 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, Zydus 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 Zydus 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 Zydus' 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 Zydus 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 Zydus 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

Digitally signed by John Ibrahim
Date: 7/09/2024 12:37:45PM
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 213719

LABELING

UPC-e-barcode: 145206

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 tablets 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 reduces NT-proBNP and is 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 mg/26 mg; 49 mg/51 mg; 97 mg/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 Zydus Pharmaceuticals (USA) Inc. at 1-877-993-8779 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----**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: 06/2024

-----**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)

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FULL PRESCRIBING INFORMATION

WARNING: FETAL TOXICITY

- When pregnancy is detected, discontinue sacubitril and valsartan tablets 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.

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

1.2 Pediatric Heart Failure

Sacubitril and valsartan tablets is indicated 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 reduces NT-proBNP and is expected to improve cardiovascular outcomes.

2 DOSAGE AND ADMINISTRATION

2.1 General Considerations

Sacubitril and valsartan tablets are contraindicated with concomitant use of an angiotensin-converting enzyme (ACE) inhibitor. If switching from an ACE inhibitor to sacubitril and valsartan tablets allow a washout period of 36 hours between administration of the two drugs [*see Contraindications (4) and Drug Interactions (7.1)*].

2.2 Adult Heart Failure

The recommended starting dose of sacubitril and valsartan tablet is 49 mg/51 mg orally twice-daily.

Double the dose of sacubitril and valsartan tablets after 2 weeks to 4 weeks to the target maintenance dose of 97 mg/103 mg twice daily, as tolerated by the patient.

2.3 Pediatric Heart Failure

For the recommended dosage for pediatric patients aged 1 year and older, refer to Table 1.

Take the recommended dose orally twice daily. Adjust pediatric patient doses every 2 weeks, as tolerated by the patient.

Table 1
Recommended Dose and Titration for Pediatric Patients Using Tablets

Weight (kg)	Titration Step Dose (twice daily)		
	Starting	Second	Final
Less than 40 kg [†]	1.6 mg/kg	2.3 mg/kg	3.1 mg/kg
At least 40 kg, less than 50 kg	24 mg/26 mg	49 mg/51 mg	72 mg/78 mg [‡]
At least 50 kg	49 mg/51 mg	72 mg/78 mg [‡]	97 mg/103 mg

[†]Use of the oral suspension is recommended in these patients. Recommended mg/kg doses are of the combined amount of both sacubitril and valsartan [see *Dosage and Administration (2.4)*].

[‡]Doses of 72 mg/78 mg can be achieved using three 24 mg/26 mg tablets [see *Dosage Forms and Strengths (3)*].

2.4 Preparation of Oral Suspension Using Tablets

Sacubitril and valsartan oral suspension can be substituted at the recommended tablet dosage in patients unable to swallow tablets.

Sacubitril and valsartan 800 mg/200 mL oral suspension can be prepared in a concentration of 4 mg/mL (sacubitril/valsartan 1.96/2.04 mg/mL). Use sacubitril and valsartan 49/51 mg tablets in the preparation of the suspension.

To make an 800 mg/200 mL (4 mg/mL) oral suspension, transfer eight tablets of sacubitril and valsartan 49/51 mg film-coated tablets into a mortar. Crush the tablets into a fine powder using a pestle. Add 60 mL of Ora-Plus[®] into the mortar and triturate gently with pestle for 10 minutes, to form a uniform suspension. Add 140 mL of Ora-Sweet[®] SF into mortar and triturate with pestle for another 10 minutes, to form a uniform suspension. Transfer the entire contents from the mortar into a clean 200 mL amber colored PET or glass bottle. Place a press-in bottle adapter and close the bottle with a child resistant cap.

The oral suspension can be stored for up to 15 days. Do not store above 25°C (77°F) and do not refrigerate. Shake before each use.

*Ora-Sweet SF[®] and Ora-Plus[®] are registered trademarks of Paddock Laboratories, Inc.

2.6 Dose Adjustment for Patients Not Taking an ACE inhibitor or ARB or Previously Taking Low Doses of These Agents

In patients not currently taking an ACE inhibitor or an angiotensin II receptor blocker (ARB) and for patients previously taking low doses of these agents, start sacubitril and valsartan tablets at half the usually recommended starting dose. After initiation, increase the dose every 2 to 4 weeks in adults and every 2 weeks in pediatric patients 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)*].

2.7 Dose Adjustment for Severe Renal Impairment

In adult and pediatric patients with severe renal impairment estimated glomerular filtration rate (eGFR less than 30 mL/min/1.73 m²), start sacubitril and valsartan tablets at half the usually recommended starting dose. After initiation, increase 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 or moderate renal impairment.

2.8 Dose Adjustment for Hepatic Impairment

In adult and pediatric patients with moderate hepatic impairment (Child-Pugh B classification), start sacubitril and valsartan tablets at half the usually recommended starting dose. After initiation, increase the dose to follow the recommended dose escalation thereafter [see *Dosage and Administration* (2.2, 2.3)].

Note: Initiate pediatric patients weighing 40 kg 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 available in following strengths:

- Sacubitril and valsartan tablets 24 mg/26 mg, (sacubitril 24 mg and valsartan 26 mg) are white to off-white colored, film-coated, oval shaped tablets and debossed with “~~1272~~” on one side and plain on the other side.
- Sacubitril and valsartan tablets 49 mg/51 mg, (sacubitril 49 mg and valsartan 51 mg) are brown to dark-brown colored, film-coated, oval shaped tablets and debossed with “~~1273~~” on one side and plain on the other side.
- Sacubitril and valsartan tablets 97 mg/103 mg, (sacubitril 97 mg and valsartan 103 mg) are light orange to orange colored, film-coated, oval shaped tablets debossed with “**1274**” on one side and plain on the other side.

4 CONTRAINDICATIONS

Sacubitril and valsartan tablets are contraindicated:

- in patients with hypersensitivity to any component
- in patients with a history of angioedema related to previous ACE inhibitor or ARB therapy [see *Warnings and Precautions* (5.2)]
- with concomitant use of ACE inhibitors. Do not administer within 36 hours of

- switching from or to an ACE inhibitor [*see Drug Interactions (7.1)*]
- with concomitant use of aliskiren in patients with diabetes [*see Drug Interactions (7.1)*]

5 WARNINGS AND PRECAUTIONS

5.1 Fetal Toxicity

Sacubitril and valsartan tablets can cause fetal harm when administered to a pregnant woman. Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. When pregnancy is detected, consider alternative drug treatment and discontinue sacubitril and valsartan tablets. However, if there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system, and if the drug is considered lifesaving for the mother, advise a pregnant woman of the potential risk to the fetus [*see Use in Specific Populations (8.1)*].

5.2 Angioedema

Sacubitril and valsartan tablets may cause angioedema [*see Adverse Reactions (6.1)*]. If angioedema occurs, discontinue sacubitril and valsartan tablets immediately, provide appropriate therapy, and monitor for airway compromise. Sacubitril and valsartan tablets must not be re-administered. In cases of confirmed angioedema where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms.

Angioedema associated with laryngeal edema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, administer appropriate therapy, e.g., subcutaneous epinephrine/adrenaline solution 1:1,000 (0.3 mL to 0.5 mL) and take measures necessary to ensure maintenance of a patent airway.

Sacubitril and valsartan tablets have been associated with a higher rate of angioedema in Black than in non-Black patients.

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

5.3 Hypotension

Sacubitril and valsartan tablets lowers blood pressure and may cause symptomatic hypotension [*see Adverse Reactions (6.1)*]. Patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients (e.g., those being treated with high doses of diuretics), are at greater risk. Correct volume or salt depletion prior to administration of sacubitril and valsartan tablets or start at a lower dose. If hypotension occurs, consider dose adjustment of diuretics, concomitant antihypertensive drugs, and treatment of other causes of hypotension (e.g., hypovolemia). If hypotension persists despite such measures, reduce the dosage or temporarily discontinue sacubitril and

valsartan tablets. Permanent discontinuation of therapy is usually not required.

5.4 Impaired Renal Function

As a consequence of inhibiting the renin-angiotensin-aldosterone system (RAAS), decreases in renal function may be anticipated in susceptible individuals treated with sacubitril and valsartan tablets [see *Adverse Reactions (6.1)*]. In patients whose renal function depends upon the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with ACE inhibitors and angiotensin receptor antagonists has been associated with oliguria, progressive azotemia and, rarely, acute renal failure and death. Closely monitor serum creatinine, and down-titrate or interrupt sacubitril and valsartan tablets in patients who develop a clinically significant decrease in renal function [see *Use in Specific Populations (8.7)* and *Clinical Pharmacology (12.3)*].

As with all drugs that affect the RAAS, sacubitril and valsartan tablets may increase blood urea and serum creatinine levels in patients with bilateral or unilateral renal artery stenosis. In patients with renal artery stenosis, monitor renal function.

5.5 Hyperkalemia

Through its actions on the RAAS, hyperkalemia may occur with sacubitril and valsartan tablets [see *Adverse Reactions (6.1)*]. Monitor serum potassium periodically and treat appropriately, especially in patients with risk factors for hyperkalemia such as severe renal impairment, diabetes, hypoaldosteronism, or a high potassium diet. Dosage reduction or interruption of sacubitril and valsartan tablets may be required [see *Dosage and Administration (2.7)*].

5.6 Risk of Allergic Reactions Due to Tartrazine

The 97 mg/103 mg tablets contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

6 ADVERSE REACTIONS

Clinically significant adverse reactions that appear in other sections of the labeling include:

- Angioedema [see *Warnings and Precautions (5.2)*]
- Hypotension [see *Warnings and Precautions (5.3)*]
- Impaired Renal Function [see *Warnings and Precautions (5.4)*]
- Hyperkalemia [see *Warnings and Precautions (5.5)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

A total of 6,622 heart failure patients were treated with sacubitril and valsartan tablets in

the PARADIGM-HF (vs. enalapril) and PARAGON-HF (vs. valsartan) clinical trials. Of these, 5,085 were exposed for at least 1 year.

Adult Heart Failure

In PARADIGM-HF, patients were required to complete sequential enalapril and sacubitril and valsartan tablets run-in periods of (median) 15 and 29 days, respectively, prior to entering the randomized double-blind period comparing sacubitril and valsartan tablets and enalapril. During the enalapril run-in period, 1,102 patients (10.5%) were permanently discontinued from the study, 5.6% because of an adverse event, most commonly renal dysfunction (1.7%), hyperkalemia (1.7%) and hypotension (1.4%). During the sacubitril and valsartan tablets run-in period, an additional 10.4% of patients permanently discontinued treatment, 5.9% because of an adverse event, most commonly renal dysfunction (1.8%), hypotension (1.7%) and hyperkalemia (1.3%). Because of this run-in design, the adverse reaction rates described below are lower than expected in practice.

In the double-blind period, safety was evaluated in 4,203 patients treated with sacubitril and valsartan tablets and 4,229 treated with enalapril. In PARADIGM-HF, patients randomized to sacubitril and valsartan tablets received treatment for up to 4.3 years, with a median duration of exposure of 24 months; 3,271 patients were treated for more than one year. Discontinuation of therapy because of an adverse event during the double-blind period occurred in 450 (10.7%) of sacubitril and valsartan tablets treated patients and 516 (12.2%) of patients receiving enalapril.

Adverse reactions occurring at an incidence of greater than or equal to 5% in patients who were treated with sacubitril and valsartan tablets in the double-blind period of PARADIGM-HF are shown in Table 3.

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

Orthostasis was reported in 2.1% of patients treated with sacubitril and valsartan tablets 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 sacubitril and valsartan tablets compared to 1.3% of patients treated with enalapril.

Table 3
Adverse Reactions Reported in greater than or equal to 5% of Patients Treated with Sacubitril and Valsartan Tablets in the Double-Blind Period of PARADIGM-HF

	Sacubitril and Valsartan Tablets	Enalapril (n = 4,229)

	(n = 4,203) %	%
Hypotension	18	12
Hyperkalemia	12	14
Cough	9	13
Dizziness	6	5
Renal failure/acute renal failure	5	5

In PARAGON-HF, no new adverse reactions were identified.

Pediatric Heart Failure

The adverse reactions observed in pediatric patients 1 year to less than 18 years old who received treatment with sacubitril and valsartan tablets were consistent with those observed in adult patients.

Laboratory Abnormalities

Hemoglobin and Hematocrit

Decreases in hemoglobin/hematocrit of greater than 20% were observed in approximately 5% of both sacubitril and valsartan tablets- and enalapril-treated patients in the double-blind period in PARADIGM-HF. Decreases in hemoglobin/hematocrit of greater than 20% were observed in approximately 7% of sacubitril and valsartan tablets-treated patients and 9% of valsartan-treated patients in the double-blind period in PARAGON-HF.

Serum Creatinine

During the double-blind period in PARADIGM-HF, approximately 16% of both sacubitril and valsartan tablets- and enalapril-treated patients had increases in serum creatinine of greater than 50%. During the double-blind period in PARAGON-HF, approximately 17% of sacubitril and valsartan tablets-treated patients and 21% of valsartan-treated patients had increases in serum creatinine of greater than 50%.

Serum Potassium

During the double-blind period of PARADIGM-HF, approximately 16% of both sacubitril and valsartan tablets- and enalapril-treated patients had potassium concentrations greater than 5.5 mEq/L. During the double-blind period of PARAGON-HF, approximately 18% of sacubitril and valsartan tablets-treated patients and 20% of valsartan-treated patients had potassium concentrations greater than 5.5 mEq/L.

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

7 DRUG INTERACTIONS

7.1 Dual Blockade of the Renin-Angiotensin-Aldosterone System

Concomitant use of sacubitril and valsartan tablets with an ACE inhibitor is contraindicated because of the increased risk of angioedema [see *Contraindications (4)*].

Avoid use of sacubitril and valsartan tablets with an ARB, because sacubitril and valsartan tablets contains the angiotensin II receptor blocker valsartan.

The concomitant use of sacubitril and valsartan tablets with aliskiren is contraindicated in patients with diabetes [see *Contraindications (4)*]. Avoid use with aliskiren in patients with renal impairment (eGFR less than 60 mL/min/1.73 m²).

7.2 Potassium-Sparing Diuretics

As with other drugs that block angiotensin II or its effects, concomitant use of potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium [see *Warnings and Precautions (5.5)*].

7.3 Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) Including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors)

In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, concomitant use of NSAIDs, including COX-2 inhibitors, with sacubitril and valsartan tablets may result in worsening of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically.

7.4 Lithium

Increases in serum lithium concentrations and lithium toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists. Monitor serum lithium levels during concomitant use with sacubitril and valsartan tablets.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Sacubitril and valsartan tablets can cause fetal harm when administered to a pregnant woman. Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death (*see Clinical Considerations*). Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. In animal reproduction studies, sacubitril and valsartan tablets treatment during organogenesis resulted in increased embryo-fetal lethality in rats and rabbits and teratogenicity in rabbits (*see Data*). When pregnancy is detected, consider alternative drug treatment and discontinue sacubitril and valsartan tablets. However, if there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system, and if the drug is considered lifesaving for the mother, advise a pregnant woman of the potential risk to the fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Oligohydramnios in pregnant women who use drugs affecting the renin-angiotensin system in the second and third trimesters of pregnancy can result in the following: reduced fetal renal function leading to anuria and renal failure, fetal lung hypoplasia, skeletal deformations, including skull hypoplasia, hypotension, and death.

Perform serial ultrasound examinations to assess the intra-amniotic environment. Fetal testing may be appropriate, based on the week of gestation. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. If oligohydramnios is observed, consider alternative drug treatment. Closely observe neonates with histories of *in utero* exposure to sacubitril and valsartan tablets for hypotension, oliguria, and hyperkalemia. In neonates with a history of *in utero* exposure to sacubitril and valsartan tablets, if oliguria or hypotension occurs, support blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and replacing renal function.

Data

Animal Data

Sacubitril and valsartan tablets treatment during organogenesis resulted in increased embryo-fetal lethality in rats at doses greater than or equal to 49 mg sacubitril/51 mg valsartan/kg/day (less than or equal to 0.06 [LBQ657, the active metabolite] and 0.72 [valsartan]-fold the maximum recommended human dose [MRHD] of 97 mg/103 mg twice-daily on the basis of the area under the plasma drug concentration-time curve [AUC]) and rabbits at doses greater than or equal to 5 mg sacubitril/5 mg valsartan/kg/day (2-fold and 0.03-fold the MRHD on the basis of valsartan and LBQ657 AUC, respectively). Sacubitril and valsartan tablets are teratogenic based on a low incidence of fetal hydrocephaly, associated with maternally toxic doses, which was observed in rabbits at a sacubitril and valsartan tablet dose of greater than or equal to 5 mg sacubitril/5 mg valsartan/kg/day. The adverse embryo-fetal effects of sacubitril and valsartan tablets are attributed to the angiotensin receptor antagonist activity.

Pre- and postnatal development studies in rats at sacubitril doses up to 750 mg/kg/day (2.2-fold the MRHD on the basis of LBQ657 AUC) and valsartan at doses up to 600 mg/kg/day (0.86-fold the MRHD on the basis of AUC) indicate that treatment with sacubitril and valsartan tablets during organogenesis, gestation and lactation may affect pup development and survival.

8.2 Lactation

Risk Summary

There is no information regarding the presence of sacubitril/valsartan in human milk, the effects on the breastfed infant, or the effects on milk production. Sacubitril/valsartan is present in rat milk (*see Data*). Because of the potential for serious adverse reactions in breastfed infants from exposure to sacubitril/valsartan, advise a nursing woman that breastfeeding is not recommended during treatment with sacubitril and valsartan tablets.

Data

Following an oral dose (15 mg sacubitril/15 mg valsartan/kg) of [¹⁴C] sacubitril and valsartan tablets to lactating rats, transfer of LBQ657 into milk was observed. After a single oral administration of 3 mg/kg [¹⁴C] valsartan to lactating rats, transfer of valsartan into milk was observed.

8.4 Pediatric Use

The safety and effectiveness of sacubitril and valsartan tablets have been established for the treatment of heart failure in pediatric patients 1 year to less than 18 years. Use of sacubitril and valsartan tablets was evaluated in a multinational, randomized, double-blind trial comparing sacubitril and valsartan tablets and enalapril in 375 patients aged 1 month to less than 18 years (Sacubitril and valsartan tablets n = 187; Enalapril n = 188) (PANORAMA-HF) [*see Clinical Studies (14.2)*]. The safety profile in pediatric patients (1 year to less than 18 years) receiving sacubitril and valsartan tablets was similar to that seen in adult patients.

Limited safety and efficacy data in patients aged 1 month to less than 1 year were inadequate to support conclusions on safety and efficacy in this age group.

Juvenile Animal Toxicity Data

Sacubitril given orally to juvenile rats from postnatal day (PND) 7 to PND 35 or PND 70 (an age approximately equivalent to neonatal through pre-pubertal development or adulthood in humans) at doses greater than or equal to 400 mg/kg/day (approximately 2-fold the AUC exposure to the active metabolite of sacubitril, LBQ657, at a sacubitril and valsartan tablets pediatric clinical dose of 3.1 mg/kg twice daily) resulted in decreases in body weight, bone length and bone mass. The decrease in body weight was transient from PND 10 to PND 20 and the effects for most bone parameters were reversible after treatment stopped. Exposure at the No-Observed-Adverse-Effect-Level (NOAEL) of 100 mg/kg/day was approximately 0.5-fold the AUC exposure to LBQ657 at the 3.1 mg/kg twice daily dose of sacubitril and valsartan tablets. The mechanism underlying bone effects in rats and the translatability to pediatric patients are unknown.

Valsartan given orally to juvenile rats from PND 7 to PND 70 (an age approximately equivalent to neonatal through adulthood in humans) produced persistent, irreversible kidney damage at all dose levels (lowest tested dose of 1 mg/kg/day). Exposure at the lowest tested dose of 1 mg/kg/day was approximately 0.2-fold the exposure at 3.1 mg/kg twice daily dose of sacubitril and valsartan tablets based on AUC. These kidney effects in neonatal rats represent expected exaggerated pharmacological effects that are observed if rats are treated during the first 13 days of life. This period coincides with 36 weeks of

gestation in humans, which could occasionally extend up to 44 weeks after conception in humans. In humans, nephrogenesis is thought to be complete around birth; however, maturation of other aspects of kidney function (such as glomerular filtration and tubular function) may continue until approximately 2 years of age. It is unknown whether post-natal use of valsartan before maturation of renal function is complete has long-term deleterious effects on the kidney.

8.5 Geriatric Use

There were 4,143 and 3,971 heart failure patients 65 years of age and older in PARADIGM-HF and PARAGON-HF, respectively [see *Clinical Studies (14)*]. Of the total number of sacubitril and valsartan tablets treated patients, 2,087 (49.6%) and 1,995 (82.9%) were 65 years of age and older, while 786 (18.7%) and 1,100 (45.7%) were 75 years of age and older in PARADIGM-HF and PARAGON-HF, respectively. No overall differences in safety or effectiveness of sacubitril and valsartan tablets have been observed between patients 65 years of age and older and younger adult patients in either study.

No relevant pharmacokinetic differences have been observed in elderly (≥ 65 years) or very elderly (≥ 75 years) patients compared to the overall population [see *Clinical Pharmacology (12.3)*].

8.6 Hepatic Impairment

No dose adjustment is required when administering sacubitril and valsartan tablets to patients with mild hepatic impairment (Child-Pugh A classification). Half of the starting dose is recommended in adult and pediatric patients with heart failure and with moderate hepatic impairment (Child-Pugh B classification). The use of sacubitril and valsartan tablets in patients with severe hepatic impairment (Child-Pugh C classification) is not recommended, as no studies have been conducted in these patients [see *Dosage and Administration (2.8)* and *Clinical Pharmacology (12.3)*].

8.7 Renal Impairment

No dose adjustment is required in patients with mild (eGFR 60 mL/min/1.73 m² to 90 mL/min/1.73 m²) to moderate (eGFR 30 mL/min/1.73 m² to 60 mL/min/1.73 m²) renal impairment. Half of the starting dose is recommended in adult and pediatric patients with heart failure and with severe renal impairment (eGFR less than 30 mL/min/1.73 m²). [see *Dosage and Administration (2.7)*, *Warnings and Precautions (5.4)* and *Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

Limited data are available with regard to overdosage in human subjects with sacubitril and valsartan tablets. In healthy volunteers, a single dose of sacubitril and valsartan tablets 583 mg sacubitril/617 mg valsartan, and multiple doses of 437 mg sacubitril/463 mg valsartan (14 days) have been studied and were well tolerated.

Hypotension is the most likely result of overdosage due to the blood pressure lowering effects of sacubitril and valsartan tablets. Symptomatic treatment should be provided.

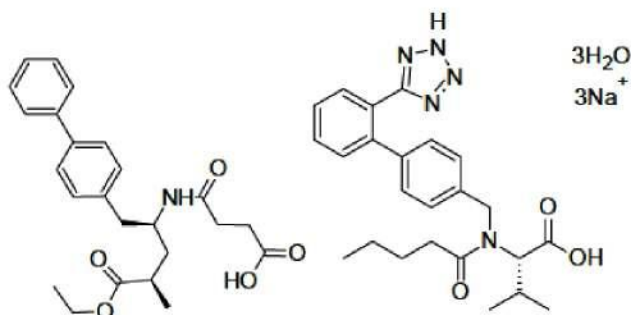
Sacubitril and valsartan tablets are unlikely to be removed by hemodialysis because of high protein binding.

11 DESCRIPTION

Sacubitril and valsartan tablets are a combination of sacubitril, a neprilysin inhibitor, and valsartan, an angiotensin II receptor blocker.

Sacubitril and valsartan tablets contain a complex comprised of anionic forms of sacubitril and valsartan, sodium cations, and water molecules in the molar ratio of 1:1:3:3, respectively. Following oral administration, the complex dissociates into sacubitril (which is further metabolized to LBQ657) and valsartan. The complex is chemically described as Trisodium [3-((1S,3R)-1-biphenyl-4-yl methyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3-methyl-2-(pentanoyl{2-(tetrazol-5-ylate)biphenyl-4-ylmethyl} amino)butyrate] trihydrate.

Its molecular formula (trihydrate) is $C_{48}H_{55}N_6O_8Na_3 \cdot 3H_2O$. Its molecular mass is 967 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. Each film-coated tablet contains following inactive ingredients: colloidal silicon dioxide, crospovidone, hypromellose, low substituted hydroxypropylcellulose, microcrystalline cellulose, polyethylene glycol, sodium stearyl fumarate and titanium dioxide.

Additionally, each 49 mg/51 mg tablet contains ferrousferrous oxide, iron oxide red and iron oxide yellow and each 97 mg/103 mg tablet contains FD&C blue #2 Aluminum Lake, FD&C red #40 Aluminum Lake and FD&C yellow #5 (tartrazine) Aluminum Lake.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Sacubitril and valsartan tablet contains a neprilysin inhibitor, sacubitril, and an angiotensin receptor blocker, valsartan. Sacubitril and valsartan tablets inhibit neprilysin (neutral endopeptidase; NEP) via LBQ657, the active metabolite of the prodrug

sacubitril, and blocks the angiotensin II type-1 (AT₁) receptor via valsartan. The cardiovascular and renal effects of sacubitril and valsartan tablets in heart failure patients are attributed to the increased levels of peptides that are degraded by neprilysin, such as natriuretic peptides, by LBQ657, and the simultaneous inhibition of the effects of angiotensin II by valsartan. Valsartan inhibits the effects of angiotensin II by selectively blocking the AT₁ receptor, and also inhibits angiotensin II-dependent aldosterone release.

12.2 Pharmacodynamics

The pharmacodynamic effects of sacubitril and valsartan tablets were evaluated after single and multiple dose administrations in healthy subjects and in patients with heart failure, and are consistent with simultaneous neprilysin inhibition and renin-angiotensin system blockade.

In a 7-day valsartan-controlled study in patients with reduced ejection fraction (HFrEF), administration of sacubitril and valsartan tablets resulted in a significant non-sustained increase in natriuresis, increased urine cGMP, and decreased plasma MR-proANP and NT-proBNP compared to valsartan.

In a 21-day study in HFrEF patients, sacubitril and valsartan tablets significantly increased urine ANP and cGMP and plasma cGMP, and decreased plasma NT-proBNP, aldosterone and endothelin-1. Sacubitril and valsartan tablets also blocked the AT₁-receptor as evidenced by increased plasma renin activity and plasma renin concentrations. In PARADIGM-HF, sacubitril and valsartan tablets decreased plasma NT-proBNP (not a neprilysin substrate) and increased plasma BNP (a neprilysin substrate) and urine cGMP compared with enalapril.

In PARAMOUNT, a randomized, double-blind, 36-week study in patients with heart failure with LVEF greater than or equal to 45% comparing 97/103 mg of sacubitril and valsartan tablets (n=149) to 160 mg of valsartan (n =152) twice-daily, sacubitril and valsartan tablets decreased NT-proBNP by 17% while valsartan increased NT-proBNP by 8% at Week 12 (p = 0.005).

In PARAGON-HF, sacubitril and valsartan tablets decreased NT-proBNP by 24% (Week 16) and 19% (Week 48) compared to 6% and 3% reductions on valsartan, respectively.

In PANORAMA-HF, a reduction in NT-proBNP was observed at Weeks 4 and 12 for sacubitril and valsartan tablets (40% and 50%) compared to baseline. The NT-proBNP levels continued to decrease over the duration of the study with a reduction of 65% for sacubitril and valsartan tablets at Week 52 compared to baseline.

QT Prolongation: In a thorough QTc clinical study in healthy male subjects, single doses of sacubitril and valsartan tablets 194 mg sacubitril/206 mg valsartan and 583 mg sacubitril/617 mg valsartan had no effect on cardiac repolarization.

Amyloid-β: Neprilysin is one of multiple enzymes involved in the clearance of amyloid-β (Aβ) from the brain and cerebrospinal fluid (CSF). Administration of sacubitril and

valsartan tablets 194 mg sacubitril/206 mg valsartan once-daily for 2 weeks to healthy subjects was associated with an increase in CSF A β ₁₋₃₈ compared to placebo; there were no changes in concentrations of CSF A β ₁₋₄₀ or CSF A β ₁₋₄₂. The clinical relevance of this finding is unknown [see *Nonclinical Toxicology (13)*].

Blood Pressure: Addition of a 50 mg single dose of sildenafil to sacubitril and valsartan tablets at steady state (194 mg sacubitril/206 mg valsartan once daily for 5 days) in patients with hypertension was associated with additional blood pressure (BP) reduction (approximately 5/4 mmHg, systolic/diastolic BP) compared to administration of sacubitril and valsartan tablets alone.

Co-administration of sacubitril and valsartan tablets did not significantly alter the BP effect of intravenous nitroglycerin.

12.3 Pharmacokinetics

Absorption

Following oral administration, sacubitril and valsartan tablets dissociates into sacubitril and valsartan. Sacubitril is further metabolized to LBQ657. The peak plasma concentrations of sacubitril, LBQ657, and valsartan are reached in 0.5 hours, 2 hours, and 1.5 hours, respectively. The oral absolute bioavailability of sacubitril is estimated to be greater than or equal to 60%. The valsartan in sacubitril and valsartan tablets are more bioavailable than the valsartan in other marketed tablet formulations; 26 mg, 51 mg, and 103 mg of valsartan in sacubitril and valsartan tablets are equivalent to 40 mg, 80 mg, and 160 mg of valsartan in other marketed tablet formulations, respectively.

Following twice-daily dosing of sacubitril and valsartan tablets, steady state levels of sacubitril, LBQ657, and valsartan are reached in 3 days. At steady state, sacubitril and valsartan do not accumulate significantly, whereas LBQ657 accumulates by 1.6-fold. Sacubitril and valsartan tablets 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 sacubitril and valsartan tablet is administered with food, this decrease is not accompanied by a clinically significant reduction in the therapeutic effect. Sacubitril and valsartan tablets can therefore be administered with or without food.

Distribution

Sacubitril, LBQ657 and valsartan are highly bound to plasma proteins (94% to 97%). Based on the comparison of plasma and CSF exposures, LBQ657 crosses the blood brain barrier to a limited extent (0.28%). The average apparent volumes of distribution of valsartan and sacubitril are 75 and 103 L, 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 (less than 10%).

Elimination

Following oral administration, 52% to 68% of sacubitril (primarily as LBQ657) and approximately 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. 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.

Linearity/Nonlinearity

The pharmacokinetics of sacubitril, LBQ657, and valsartan were linear over a sacubitril and valsartan tablets dose range of 24 mg sacubitril/26 mg valsartan to 194 mg sacubitril/206 mg valsartan.

Drug Interactions:

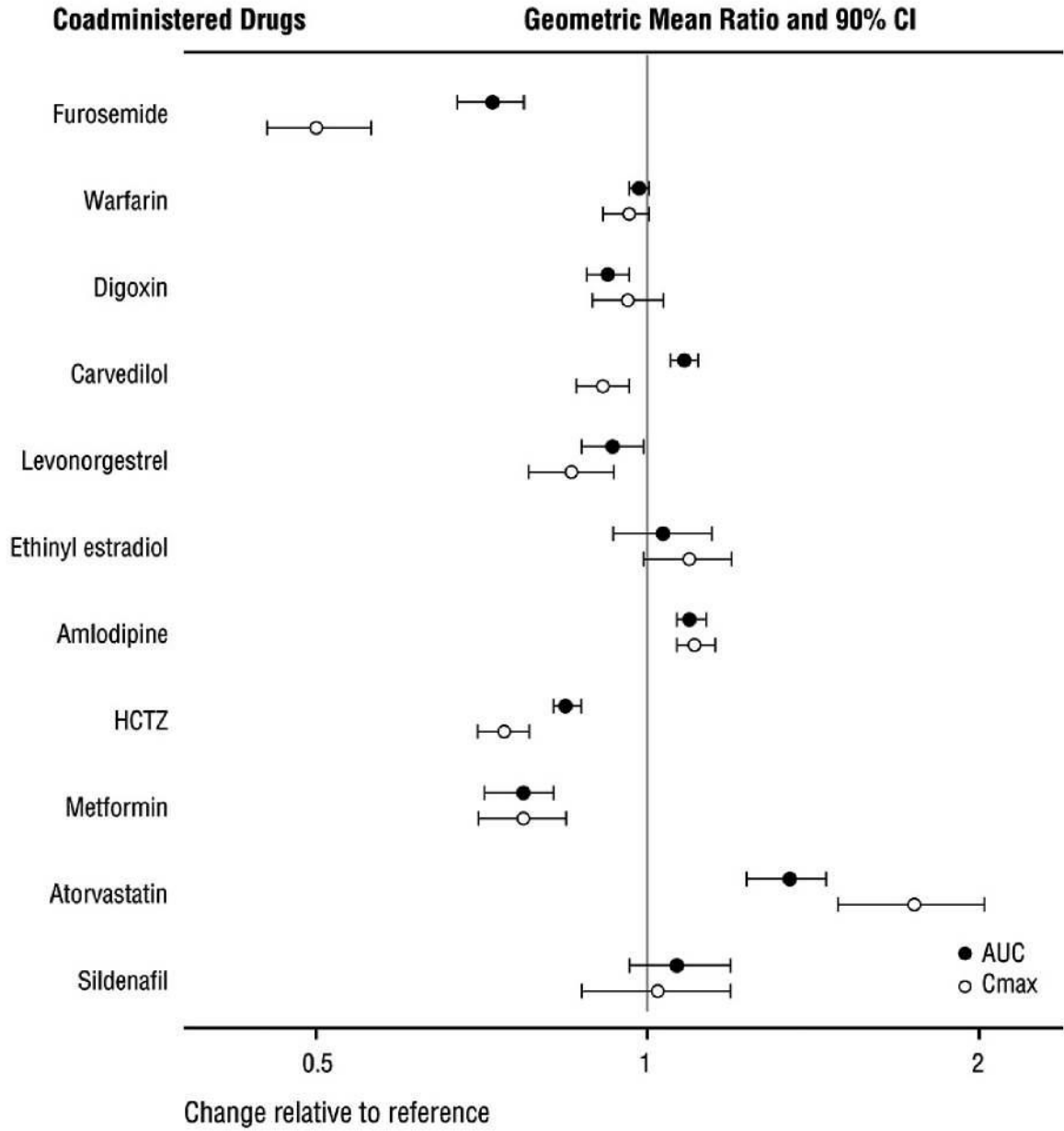
Effect of Co-administered Drugs on Sacubitril and Valsartan Tablets:

Because CYP450 enzyme-mediated metabolism of sacubitril and valsartan is minimal, coadministration with drugs that impact CYP450 enzymes is not expected to affect the pharmacokinetics of sacubitril and valsartan tablets. Dedicated drug interaction studies demonstrated that coadministration of furosemide, warfarin, digoxin, carvedilol, a combination of levonorgestrel/ethinyl estradiol, amlodipine, omeprazole, hydrochlorothiazide (HCTZ), metformin, atorvastatin, and sildenafil, did not alter the systemic exposure to sacubitril, LBQ657 or valsartan.

Effect of Sacubitril and Valsartan Tablets on Co-administered Drugs:

In vitro data indicate that sacubitril inhibits OATP1B1 and OATP1B3 transporters. The effects of sacubitril and valsartan tablets on the pharmacokinetics of coadministered drugs are summarized in Figure 1.

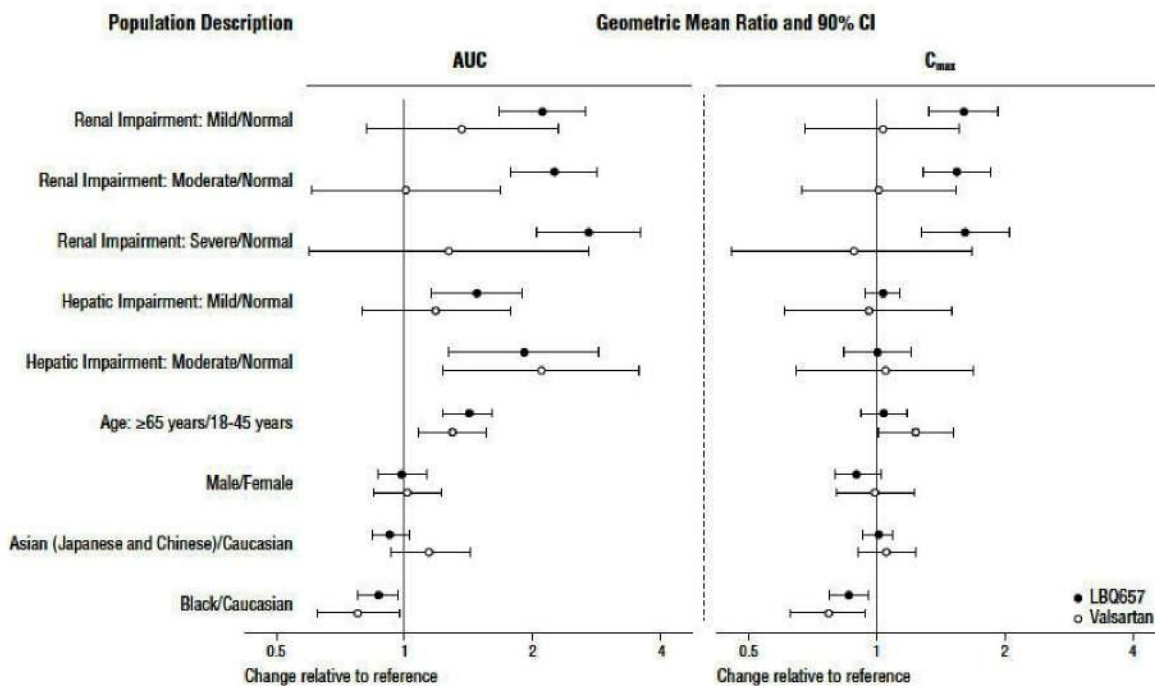
Figure 1
Effect of Sacubitril and Valsartan Tablets on Pharmacokinetics of Coadministered Drugs



Specific Populations

Effect of specific populations on the pharmacokinetics of LBQ657 and valsartan are shown in Figure 2.

Figure 2
Pharmacokinetics of Sacubitril and Valsartan Tablets in Specific Populations



Note: Child-Pugh Classification was used for hepatic impairment.

Pediatric Patients: The pharmacokinetics of sacubitril and valsartan tablets were evaluated in pediatric heart failure patients 1 to less than 18 years old administered oral doses of 0.8 mg/kg and 3.1 mg/kg of sacubitril and valsartan tablets. Pharmacokinetic data indicated that exposure to sacubitril and valsartan tablets in pediatric and adult patients is similar.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and Mutagenesis

Carcinogenicity studies conducted in mice and rats with sacubitril and valsartan did not identify any carcinogenic potential for sacubitril and valsartan tablets. The LBQ657 C_{max} at the high dose (HD) of 1,200 mg/kg/day in male and female mice was, respectively, 14 and 16 times that in humans at the MRHD. The LBQ657 C_{max} in male and female rats at the HD of 400 mg/kg/day was, respectively, 1.7 and 3.5 times that at the MRHD. The doses of valsartan studied (high dose of 160 mg/kg/day and 200 mg/kg/day in mice and rats, respectively) were about 4 and 10 times, respectively, the MRHD on a mg/m² basis.

Mutagenicity and clastogenicity studies conducted with sacubitril and valsartan tablets, sacubitril, and valsartan did not reveal any effects at either the gene or chromosome level.

Impairment of Fertility

Sacubitril and valsartan tablets did not show any effects on fertility in rats up to a dose of 73 mg sacubitril/77 mg valsartan/kg/day (≤ 1.0 -fold and ≤ 0.18 -fold the MRHD on the basis of the AUCs of valsartan and LBQ657, respectively).

13.2 Animal Toxicology and/or Pharmacology

The effects of sacubitril and valsartan tablets on amyloid- β concentrations in CSF and brain tissue were assessed in young (2 years to 4 years old) cynomolgus monkeys treated with sacubitril and valsartan tablets (24 mg sacubitril/26 mg valsartan/kg/day) for 2 weeks. In this study, sacubitril and valsartan tablets affected CSF A β clearance, increasing CSF A β 1-40, 1-42, and 1-38 levels in CSF; there was no corresponding increase in A β levels in the brain. In addition, in a toxicology study in cynomolgus monkeys treated with sacubitril and valsartan tablets at 146 mg sacubitril/154 mg valsartan/kg/day for 39 weeks, there was no amyloid- β accumulation in the brain.

14 CLINICAL STUDIES

Dosing in clinical trials was based on the total amount of both components of sacubitril and valsartan tablets, i.e., 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg were referred to as 50 mg, 100 mg, and 200 mg, respectively.

14.1 Adult Heart Failure

PARADIGM-HF

PARADIGM-HF was a multinational, randomized, double-blind trial comparing sacubitril and valsartan tablets and enalapril in 8,442 adult patients with symptomatic chronic heart failure (NYHA class II–IV) and systolic dysfunction (left ventricular ejection fraction $\leq 40\%$). Patients had to have been on an ACE inhibitor or ARB for at least four weeks and on maximally tolerated doses of beta-blockers. Patients with a systolic blood pressure of less than 100 mmHg at screening were excluded.

The primary objective of PARADIGM-HF was to determine whether sacubitril and valsartan tablets, a combination of sacubitril and an RAS inhibitor (valsartan), was superior to an RAS inhibitor (enalapril) alone in reducing the risk of the combined endpoint of cardiovascular (CV) death or hospitalization for heart failure (HF).

After discontinuing their existing ACE inhibitor or ARB therapy, patients entered sequential single-blind run-in periods during which they received enalapril 10 mg twice-daily, followed by sacubitril and valsartan tablets 100 mg twice-daily, increasing to 200 mg twice-daily. Patients who successfully completed the sequential run-in periods were randomized to receive either sacubitril and valsartan tablets 200 mg (N=4,209) twice-daily or enalapril 10 mg (N=4,233) twice-daily. The primary endpoint was the first event in the composite of CV death or hospitalization for HF. The median follow-up duration was 27 months and patients were treated for up to 4.3 years.

The population was 66% Caucasian, 18% Asian, and 5% Black; the mean age was 64 years and 78% were male. At randomization, 70% of patients were NYHA Class II, 24% were NYHA Class III, and 0.7% were NYHA Class IV. The mean left ventricular ejection fraction was 29%. The underlying cause of heart failure was coronary artery disease in 60% of patients; 71% had a history of hypertension, 43% had a history of myocardial infarction, 37% had an eGFR less than 60 mL/min/1.73 m², and 35% had diabetes mellitus. Most patients were taking beta-blockers (94%), mineralocorticoid antagonists (58%), and diuretics (82%). Few patients had an implantable cardioverter-defibrillator (ICD) or cardiac resynchronization therapy-defibrillator (CRT-D) (15%).

PARADIGM-HF demonstrated that sacubitril and valsartan tablets, a combination of sacubitril and an RAS inhibitor (valsartan), was superior to a RAS inhibitor (enalapril), in reducing the risk of the combined endpoint of cardiovascular death or hospitalization for heart failure, based on a time-to-event analysis (hazard ratio [HR] 0.80; 95% confidence interval [CI], 0.73, 0.87, $p < 0.0001$). The treatment effect reflected a reduction in both cardiovascular death and heart failure hospitalization; see Table 4 and Figure 3. Sudden death accounted for 45% of cardiovascular deaths, followed by pump failure, which accounted for 26%.

Sacubitril and valsartan tablets also improved overall survival (HR 0.84; 95% CI [0.76, 0.93], $p=0.0009$) (Table 4). This finding was driven entirely by a lower incidence of cardiovascular mortality on sacubitril and valsartan tablets.

Table 4
Treatment Effect for the Primary Composite Endpoint, its Components, and All-cause Mortality in PARADIGM-HF

	Sacubitril and Valsartan Tablets N=4,187 n (%)	Enalapril N=4,212 n (%)	Hazard Ratio (95% CI)	p-value
Primary composite endpoint of cardiovascular death or heart failure hospitalization	914 (21.8)	1,117 (26.5)	0.80 (0.73, 0.87)	<0.0001
Cardiovascular death as first event	377 (9)	459 (10.9)		
Heart failure hospitalization as first event	537 (12.8)	658 (15.6)		
Number of patients with events:*				
Cardiovascular death**	558 (13.3)	693 (16.5)	0.80 (0.71, 0.89)	
Heart failure hospitalizations	537 (12.8)	658 (15.6)	0.79 (0.71, 0.89)	
All-cause mortality	711 (17)	835 (19.8)	0.84 (0.76, 0.93)	0.0009

*Analyses of the components of the primary composite endpoint were not prospectively planned to be adjusted for multiplicity

**Includes patients who had heart failure hospitalization prior to death

The Kaplan-Meier curves presented below (Figure 3) show time to first occurrence of the primary composite endpoint (3A), and time to occurrence of cardiovascular death at any time (3B) and first heart failure hospitalization (3C).

Figure 3
Kaplan-Meier Curves for the Primary Composite Endpoint (A), Cardiovascular Death (B), and Heart Failure Hospitalization (C)

Figure A

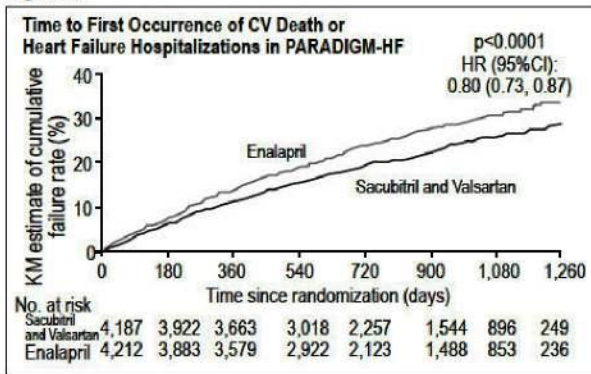


Figure B

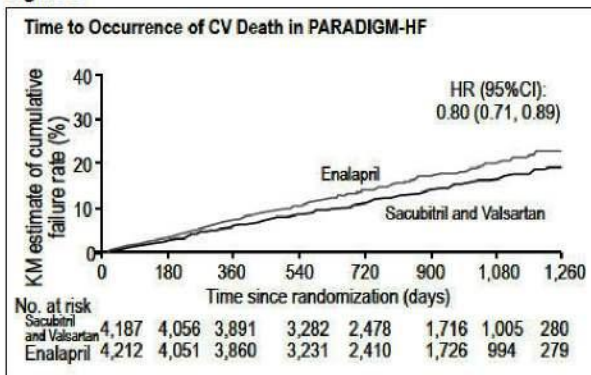
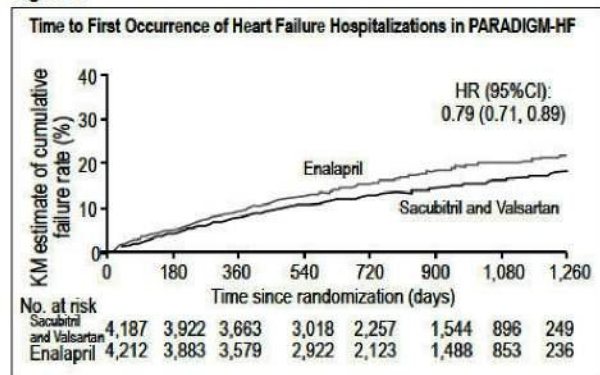
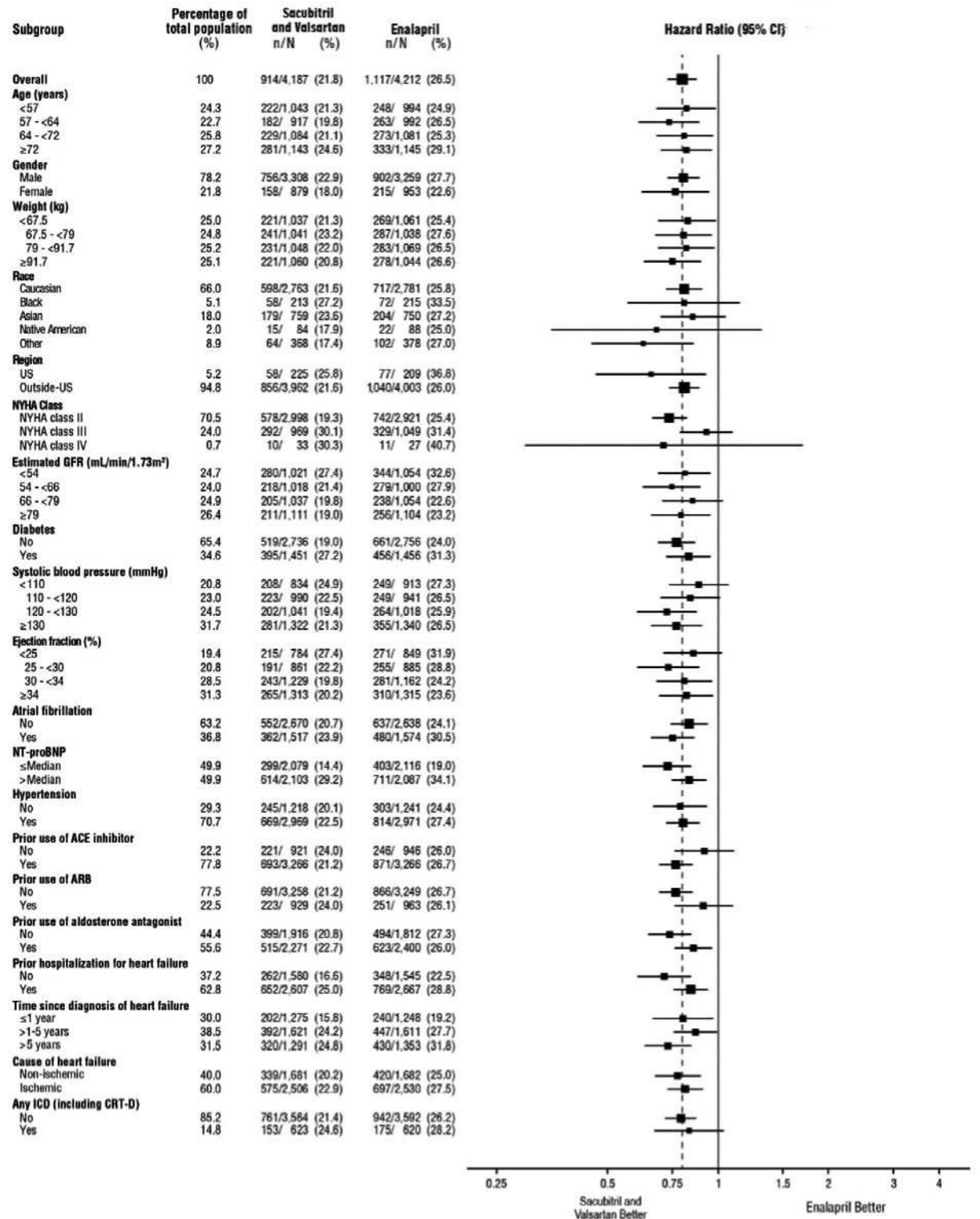


Figure C



A wide range of demographic characteristics, baseline disease characteristics, and baseline concomitant medications were examined for their influence on outcomes. The results of the primary composite endpoint were consistent across the subgroups examined (Figure 4).

Figure 4
Primary Composite Endpoint (CV Death or HF Hospitalization) - Subgroup Analysis
(PARADIGM-HF)



Note: The figure above presents effects in various subgroups, all of which are baseline characteristics. The 95% confidence limits that are shown do not take into account the number of comparisons made, and may not reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

PARAGON-HF

PARAGON-HF, was a multicenter, randomized, double-blind trial comparing sacubitril and valsartan tablets and valsartan in 4,796 adult patients with symptomatic heart failure with left ventricular ejection fraction greater than or equal to 45%, and structural heart disease [either left atrial enlargement (LAE) or left ventricular hypertrophy (LVH)]. Patients with a systolic blood pressure of less than 110 mmHg and patients with any prior echocardiographic LVEF less than 40% at screening were excluded.

The primary objective of PARAGON-HF was to determine whether sacubitril and valsartan tablets reduced the rate of the composite endpoint of total (first and recurrent) heart failure (HF) hospitalizations and cardiovascular (CV) death.

After discontinuing their existing ACE inhibitor or ARB therapy, patients entered sequential single-blind run-in periods during which they received valsartan 80 mg twice-daily, followed by sacubitril and valsartan tablets 100 mg twice-daily. Patients on prior low doses of an ACEi or ARB began the run-in period receiving valsartan 40 mg twice-daily for 1 to 2 weeks. Patients who successfully completed the sequential run-in periods were randomized to receive either sacubitril and valsartan tablets 200 mg (N = 2,419) twice-daily or valsartan 160 mg (N = 2,403) twice-daily. The median follow-up duration was 35 months and patients were treated for up to 4.7 years.

The population was 81% Caucasian, 13% Asian, and 2% Black; the mean age was 73 years and 52% were female. At randomization, 77% of patients were NYHA Class II, 19% were NYHA Class III, and 0.4% were NYHA Class IV. The median left ventricular ejection fraction was 57%. The underlying cause of heart failure was of ischemic etiology in 36% of patients. Furthermore, 96% had a history of hypertension, 23% had a history of myocardial infarction, 46% had an eGFR less than 60 mL/min/1.73 m², and 43% had diabetes mellitus. Most patients were taking beta-blockers (80%) and diuretics (95%).

PARAGON-HF demonstrated that sacubitril and valsartan tablets had a numerical reduction in the rate of the composite endpoint of total (first and recurrent) HF hospitalizations and CV death, based on an analysis using a proportional rates model (rate ratio [RR] 0.87; 95% CI [0.75, 1.01], $p = 0.06$); see Table 5. The treatment effect was primarily driven by the reduction in total HF hospitalizations in patients randomized to sacubitril and valsartan tablets (RR 0.85; 95% CI [0.72, 1.00]).

Table 5
Treatment Effect for the Primary Composite Endpoint and Its Components in PARAGON-HF

	Sacubitril and valsartan tablets N = 2,407		Valsartan N = 2,389		Effect Size (95% CI)
Efficacy Endpoints	n	Event Rate^a	n	Event Rate^a	
Composite of total (first and recurrent) HF hospitalizations and CV death	894	12.8	1,009	14.6	RR = 0.87 (0.75, 1.01) <i>p</i> -value 0.06
Total HF Hospitalizations	690	9.9	797	11.6	RR = 0.85 (0.72, 1)
CV Death ^b	204	2.9	212	3.1	HR = 0.95 (0.79, 1.16)

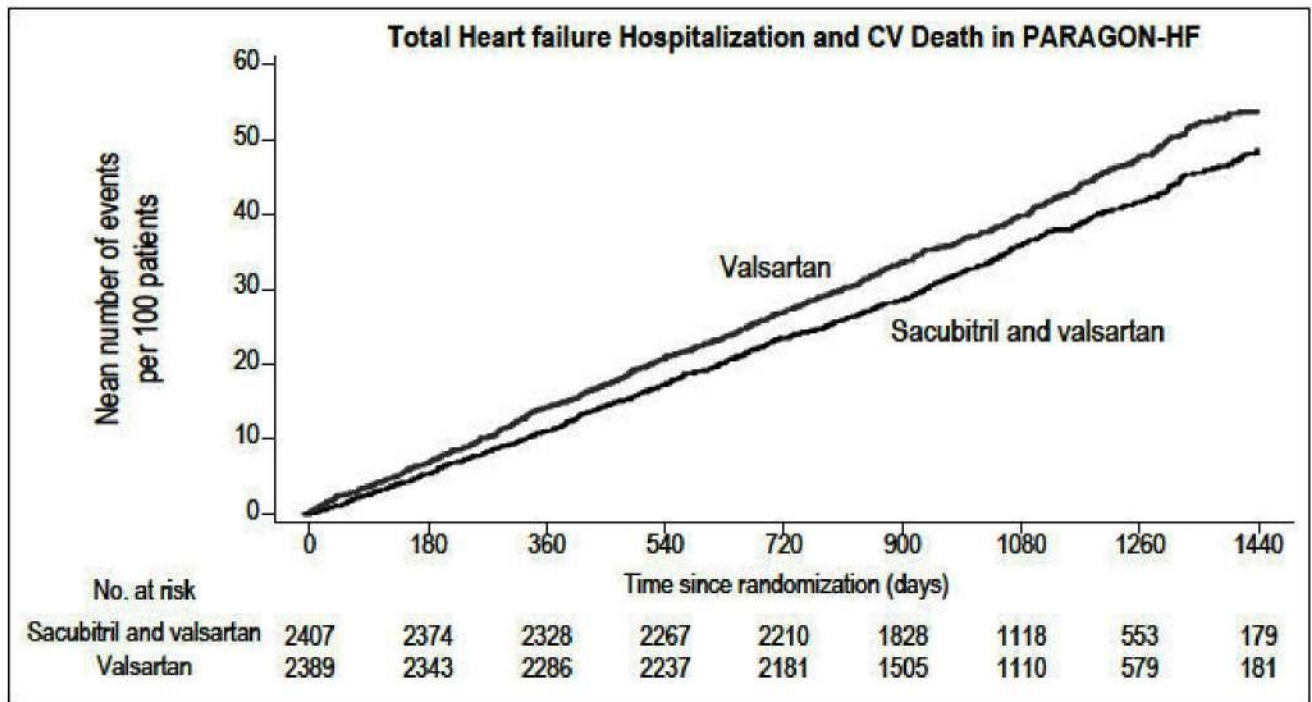
Abbreviations: RR = rate ratio, HR = hazard ratio.

^aEvent rate per 100 patient-years.

^bIncludes patients who had CV death following HF hospitalization event.

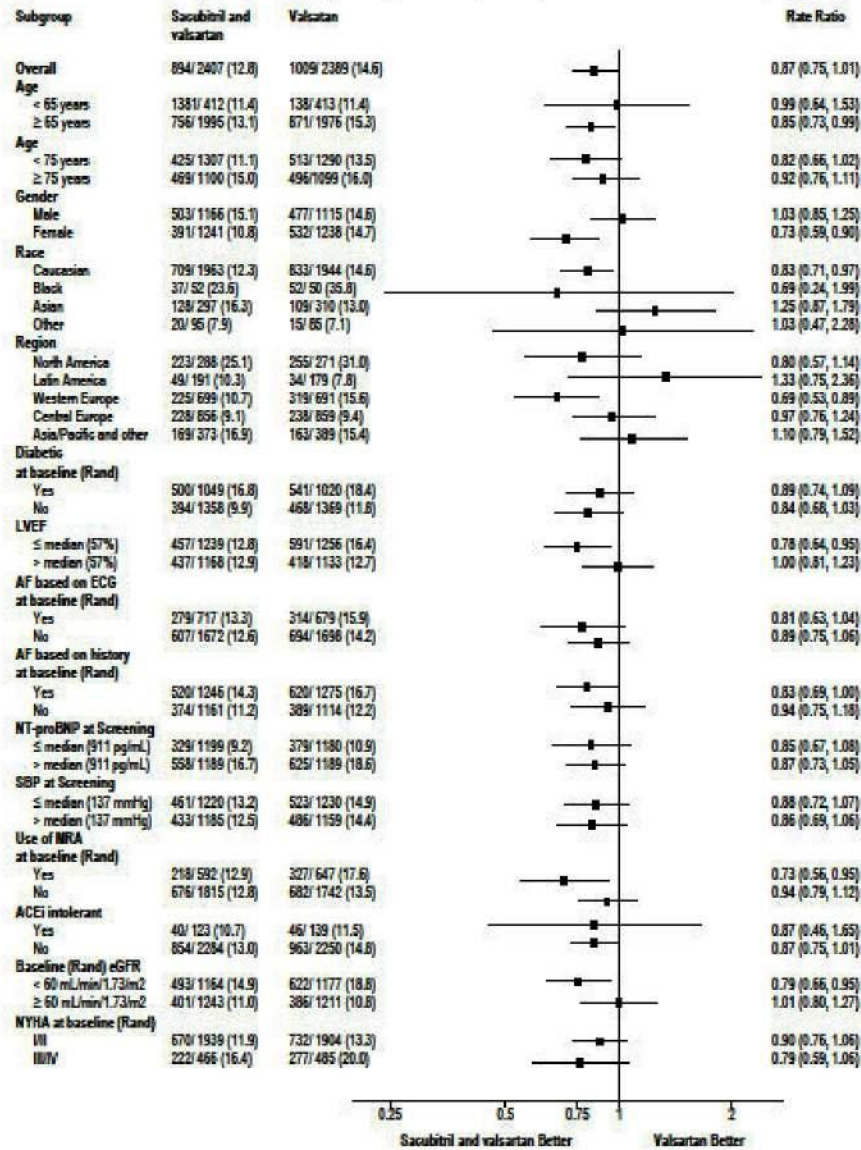
Figure 5 shows the mean number of composite endpoint events of total HF hospitalizations and CV death over time.

Figure 5
Mean Number of Events Over Time for the Primary Composite Endpoint of Total HF Hospitalizations and CV Death



A wide range of demographic characteristics, baseline disease characteristics, and baseline concomitant medications were examined for their influence on outcomes (Figure 6).

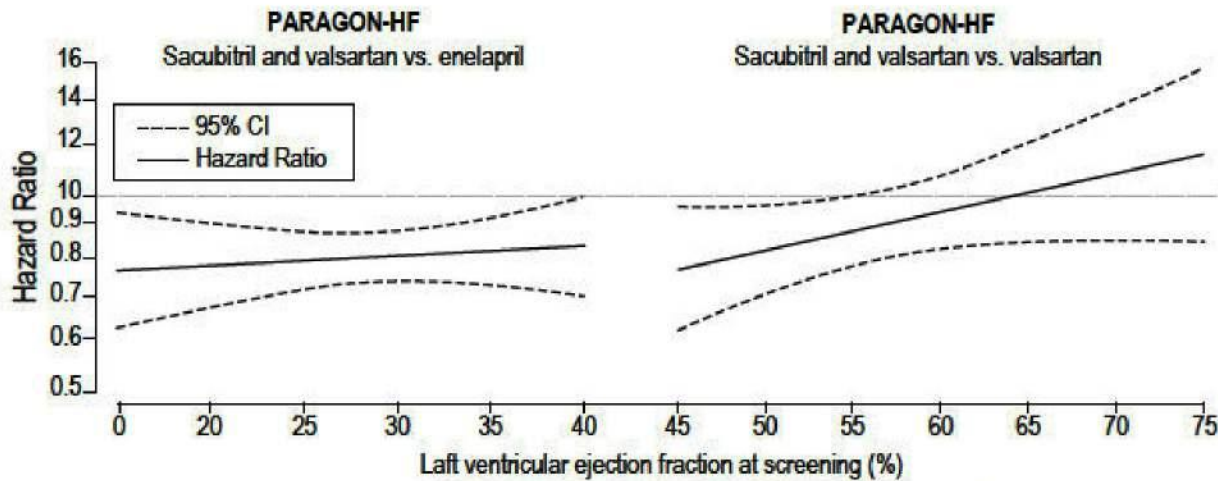
Figure 6
Primary Composite Endpoint of Total HF Hospitalizations and CV Death –
Subgroup Analysis (PARAGON-HF)



Note: The figure above presents effects in various subgroups, all of which are baseline characteristics. The 95% confidence limits that are shown do not take into account the number of comparisons made, and may not reflect the effect of a particular factor after adjustment for all other factors.

In an analysis of the relationship between LVEF and outcome in PARADIGM-HF and PARAGON-HF, patients with LVEF below normal treated with sacubitril and valsartan tablets experienced greater risk reduction (Figure 7).

Figure 7
Treatment Effect for the Composite Endpoint of Time to First HF Hospitalization or CV Death by LVEF in PARADIGM-HF and PARAGON-HF



14.2 Pediatric Heart Failure

The efficacy of sacubitril and valsartan tablets was evaluated in a multinational, randomized, double-blind trial PANORAMA-HF comparing sacubitril and valsartan tablets (n = 187) and enalapril (n = 188) in pediatric patients aged 1 month to less than 18 years old due to systemic left ventricular systolic dysfunction (LVEF ≤ 45% or fractional shortening ≤ 22.5%). Patients with systemic right ventricle, single ventricle, restrictive cardiomyopathy or hypertrophic cardiomyopathy were excluded from the trial. Efficacy of sacubitril and valsartan tablets in patients less than 1 year old was not established. At Week 52, there were 144 sacubitril and valsartan tablets and 133 enalapril patients with a post-baseline assessment of NT-proBNP. The estimated least squares mean percent reduction from baseline in NT-proBNP was 65% and 62% in the sacubitril and valsartan tablets and enalapril groups, respectively. While the between-group difference was not nominally statistically significant, the reductions for sacubitril and valsartan tablets and enalapril were larger than what was seen in adults; these reductions did not appear to be attributable to post-baseline changes in background therapy.

Because sacubitril and valsartan tablets improved outcomes and reduced NT-proBNP in adults in PARADIGM-HF, the effect on NTproBNP was the basis to infer improved cardiovascular outcomes in pediatric patients.

16 HOW SUPPLIED/STORAGE AND HANDLING

Sacubitril and valsartan tablets 24 mg/26 mg, (sacubitril 24 mg and valsartan 26 mg) are white to off-white colored, film-coated, oval shaped tablets debossed with "1272" on one side and plain on the other side and are supplied as follows:

- NDC 70710-1272-6 in bottles of 60 tablets with child-resistant closure
- NDC 70710-1272-8 in bottles of 180 tablets with child-resistant closure
- NDC 70710-1272-4 in unit-dose blister cartons of 100 tablets (10 x 10 unit-dose)

Sacubitril and valsartan tablets 49 mg/51 mg, (sacubitril 49 mg and valsartan 51 mg) are brown to dark-brown colored, film-coated, oval shaped tablets debossed with “1273” on one side and plain on the other side and are supplied as follows:

NDC 70710-1273-6 in bottles of 60 tablets with child-resistant closure

NDC 70710-1273-8 in bottles of 180 tablets with child-resistant closure

NDC 70710-1273-4 in unit-dose blister cartons of 100 tablets (10 x 10 unit-dose)

Sacubitril and valsartan tablets 97 mg/103 mg, (sacubitril 97 mg and valsartan 103 mg) are light orange to orange colored, film-coated, oval shaped tablets debossed with “1274” on one side and plain on the other side and are supplied as follows:

NDC 70710-1274-6 in bottles of 60 tablets with child-resistant closure

NDC 70710-1274-8 in bottles of 180 tablets with child-resistant closure

NDC 70710-1274-4 in unit-dose blister cartons of 100 tablets (10 x 10 unit-dose)

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

17 PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Patient Information).

Pregnancy: Advise female patients of childbearing age about the consequences of exposure to sacubitril and valsartan tablets during pregnancy. Discuss treatment options with women planning to become pregnant. Ask patients to report pregnancies to their physicians as soon as possible [see *Warnings and Precautions (5.1) and Use in Specific Populations (8.1)*].

Lactation: Advise patients that breastfeeding is not recommended during treatment with sacubitril and valsartan tablets [see *Use in Specific Populations (8.2)*].

Angioedema: Advise patients to discontinue use of their previous ACE inhibitor or ARB. Advise patients to allow a 36 hour wash-out period if switching from or to an ACE inhibitor [see *Contraindications (4) and Warnings and Precautions (5.2)*].

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Rev.: 06/24

Patient Information
Sacubitril (sak ue' bi tril) and Valsartan (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 tablet 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 Tablets work 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 is 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:**
 - Your pharmacist will prepare sacubitril and valsartan tablets for you or your child to take as a liquid suspension.
 - 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 much 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.
- Drug sacubitril and valsartan tablets come in child-resistant bottles of 60's and 180's.

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 give 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: colloidal silicon dioxide, crospovidone, hypromellose, low substituted hydroxypropylcellulose, microcrystalline cellulose, polyethylene glycol, sodium stearyl fumarate and titanium dioxide.

Additionally, each 49 mg/51 mg tablet contains ferrousferrous oxide, iron oxide red and iron oxide yellow and each 97 mg/103 mg tablet contains FD&C blue #2 Aluminum Lake, FD&C red #40 Aluminum Lake and FD&C yellow #5 (tartrazine) Aluminum Lake.

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

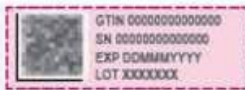
For more information, go to MedicalAffairs@zydususa.com or Tel. 1-877-993-8779.

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



Over Coding Template

No Varished Area (Do Not Print)
(18 x 41 mm)

NDC 70710-1272-6

Sacubitril and Valsartan Tablets

24 mg/26 mg

zydus

Rx only
60 Tablets

Each film-coated tablet contains 24 mg of sacubitril and 26 mg of valsartan.
Usual Dosage: See package insert for full prescribing information.
This package is child-resistant.
Store at 25°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from moisture.
Keep this and all drugs out of the reach of children.
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NDC 70710-1272-8

Sacubitril and Valsartan Tablets

24 mg/26 mg

Rx only
180 Tablets

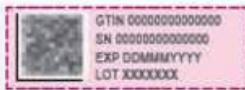
Each film-coated tablet contains 24 mg of sacubitril and 26 mg of valsartan.
 Usual Dosage: See package insert for full prescribing information.
 This package is child-resistant.
 Store at 25°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].
 Protect from moisture.
 Keep this and all drugs out of the reach of children.
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No Varished Area (Do Not Print)
(18 x 41 mm)

NDC 70710-1273-6

Sacubitril and Valsartan Tablets

49 mg/51 mg

zydus

Rx only
60 Tablets

Each film-coated tablet contains 49 mg of sacubitril and 51 mg of valsartan.
Usual Dosage: See package insert for full prescribing information.
This package is child-resistant.
Store at 25°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from moisture.
Keep this and all drugs out of the reach of children.
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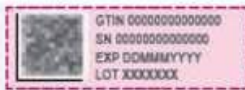
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(18 x 41 mm)

NDC 70710-1273-8

Sacubitril and Valsartan Tablets

49 mg/51 mg

zydus

Rx only
180 Tablets

Each film-coated tablet contains 49 mg of sacubitril and 51 mg of valsartan.
Usual Dosage: See package insert for full prescribing information.
This package is child-resistant.
Store at 25°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from moisture.
Keep this and all drugs out of the reach of children.
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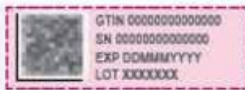
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NDC 70710-1274-6

Sacubitril and Valsartan Tablets

97 mg/103 mg

Rx only
60 Tablets

Each film-coated tablet contains 97 mg of sacubitril and 103 mg of valsartan. Contains FD&C Yellow No. 5 (tartrazine) as a color additive.
Usual Dosage: See package insert for full prescribing information.
This package is child-resistant.
Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from moisture.
Keep this and all drugs out of the reach of children.
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Rev: 0622

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NDC 70710-1274-8

Sacubitril and Valsartan Tablets

97 mg/103 mg

zydus

Rx only
180 Tablets

Each film-coated tablet contains 97 mg of sacubitril and 103 mg of valsartan.
Contains FD&C Yellow No. 5 (tartrazine) as a color additive.
Usual Dosage: See package insert for full prescribing information.
This package is child-resistant.
Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].
Protect from moisture.
Keep this and all drugs out of the reach of children.
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Rev.: 06/22

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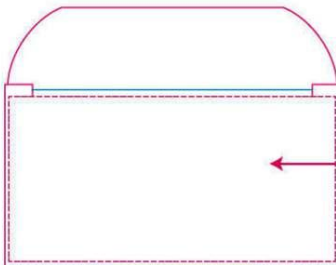
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 Sacubitril and Valsartan Tablet 97 mg/103 mg Made in INDIA Distributed by: Zydus Pharmaceuticals (USA) Inc., Pennington, NJ 08534 Lot Exp	 Sacubitril and Valsartan Tablet 97 mg/103 mg Made in INDIA Distributed by: Zydus Pharmaceuticals (USA) Inc., Pennington, NJ 08534 Lot Exp
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(b) (4)

GTIN 00000000000000
SN 00000000000000
EXP DDMMYYYY
LOT XXXXXXX

Over Coding Template



24 mg/26 mg

Sacubitril and Valsartan
Tablets

NDC 70710-1272-4

NDC 70710-1272-4

**Sacubitril and Valsartan
Tablets**

24 mg/26 mg

This unit-dose package is
not child-resistant.

For institutional use and for
households without children

zydus
Pharmaceuticals
USA
100 Tablets
(10 x 10 unit-dose)
Rx only

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

Usual Dosage: See package insert for
full prescribing information.

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

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

**Sacubitril and Valsartan
Tablets**

24 mg/26 mg

This unit-dose package is
not child-resistant.

For institutional use and for
households without children

zydus
Pharmaceuticals
USA
100 Tablets
(10 x 10 unit-dose)
Rx only



Manufactured by:
Zydus Lifesciences Ltd.
Ahmedabad, India
Distributed by:
Zydus Pharmaceuticals (USA) Inc.
Pennington, NJ 08534

Rev.: 06/22

NDC 70710-1272-4

**Sacubitril and Valsartan
Tablets**

24 mg/26 mg

zydus
Pharmaceuticals
USA
100 Tablets
(10 x 10 unit-dose)
Rx only

(b) (4)

GTIN 00000000000000
SN 00000000000000
EXP DDMMYYYY
LOT XXXXXXX

Over Coding Template

49 mg/51 mg

Sacubitril and Valsartan
Tablets

NDC 70710-1273-4

NDC 70710-1273-4

Sacubitril and
Valsartan
Tablets

49 mg/51 mg

This unit-dose package is
not child-resistant.

For institutional use and for
households without children

zydus
Pharmaceuticals
USA

100 Tablets
(10 x 10 unit-dose)

Rx only

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

Usual Dosage: See package insert for
full prescribing information.

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

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

Sacubitril and
Valsartan
Tablets

49 mg/51 mg

This unit-dose package is
not child-resistant.

For institutional use and for
households without children

zydus
Pharmaceuticals
USA

100 Tablets
(10 x 10 unit-dose)

Rx only



Rev.: 06/22

NDC 70710-1273-4

Sacubitril and Valsartan
Tablets

49 mg/51 mg

zydus
Pharmaceuticals
USA

100 Tablets
(10 x 10 unit-dose)

Rx only

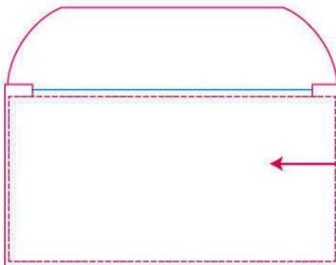
Manufactured by:
Zydus Lifesciences Ltd.
Ahmedabad, India

Distributed by:
Zydus Pharmaceuticals (USA) Inc.
Pennington, NJ 08534

(b) (4)

GTIN 00000000000000
SN 00000000000000
EXP DDDMMYYYYY
LOT XXXXXXXX

Over Coding Template



97 mg/103 mg
Tablets
Sacubitril and Valsartan

NDC 70710-1274-4

NDC 70710-1274-4

Sacubitril and Valsartan Tablets

97 mg/103 mg

This unit-dose package is not child-resistant.

For institutional use and for households without children

100 Tablets
(10 x 10 unit-dose)
zydus
Pharmaceuticals
USA
Rx only

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

Contains FD&C Yellow No. 5 (tartrazine) as a color additive.

Usual Dosage: See package insert for full prescribing information.

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

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

Sacubitril and Valsartan Tablets

97 mg/103 mg

This unit-dose package is not child-resistant.

For institutional use and for households without children

100 Tablets
(10 x 10 unit-dose)
zydus
Pharmaceuticals
USA
Rx only



Manufactured by:
Zydus Lifesciences Ltd.
Ahmedabad, India

Distributed by:
Zydus Pharmaceuticals (USA) Inc.
Pennington, NJ 08534

Rev.: 06/22

NDC 70710-1274-4

Sacubitril and Valsartan Tablets

97 mg/103 mg

100 Tablets
(10 x 10 unit-dose)
zydus
Pharmaceuticals
USA
Rx only

(b) (4)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 213719

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	June 28, 2024, and June 2, 2024
ANDA Number(s)	213719
Review Number	6
Applicant Name	Zydus Pharmaceuticals (USA) Inc.
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	June 11, 2024, June 28, 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)

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 June 11, 2024, June 28, 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)

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

(b)(4)

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	60s crc and 180s crc count for 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg Tablets	06/14/2022	Satisfactory
Blister	Final	10s	06/14/2022	Satisfactory
Carton	Final	100s	06/14/2022	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	ID 145206 Revised: 06/2024	6/28/2024	Satisfactory
Medication Guide	N/A	N/A		
Patient Information	Final	ID 145206 Revised: 06/2024	6/28/2024	Satisfactory
Instructions for Use	N/A	N/A		
SPL Data Elements				

4 LABELING REVIEW INFORMATION(C6)

4.1 REGULATORY INFORMATION (C6)

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

Yes	No	
		(b)(4)

4.2 MODEL PRESCRIBING INFORMATION (C6)

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

MOST RECENTLY APPROVED NDA MODEL LABELING

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

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

Supplement Approval Date: 04/12/2024

Proprietary Name: Entresto

Established Name: Sacubitril/Valsartan Tablets

Description of Supplement:

NDA 218591
NDA 207620/S-025

NDA APPROVAL

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

Dear Dr. Griffith:

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

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

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

- The treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older. ENTRESTO reduces NT-proBNP and is expected to improve cardiovascular outcomes.

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

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

MOST RECENTLY APPROVED ANDA MODEL LABELING

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

(b)(4)

OTHER IMPORTANT INFORMATION:

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

(b)(4)

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

Reviewer Assessment:

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

Reviewer Comments:

- (b)(4)
- S-022, S-021, and are CMC pending supplements.

C6-6/28/2024

- (b)(4)

C6-7/2/2024

(b)(4)

Deficiency Comments:

4.3 PATENTS AND EXCLUSIVITIES (C6)

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

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

Table 4: Impact of Model Labeling Patents on ANDA Labeling

Strengths	Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	11058667	05/09/2036	U-3170	TREATING CHRONIC HEART FAILURE WITH REDUCED EJECTION FRACTION IN PATIENTS NOT TAKING AN ACE INHIBITOR OR AN ARB OR PREVIOUSLY TAKING LOW DOSES OF THESE AGENTS, BY TITRATING UP FROM HALF THE USUALLY RECOMMENDED STARTING DOSE	IV	02/18/2022	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	06/28/2024	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	7468390*PED	05/27/2024			IV	07/08/2019	Expired
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	8101659	01/15/2025			IV	07/08/2019	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	8101659*PED	07/15/2025			IV	07/08/2019	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	8877938	05/27/2027			IV	07/08/2019	None
24 mg;26 mg, 49 mg;51 mg,	8877938*PED	11/27/2027			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
97 mg;103 mg							
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	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			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	IV	06/28/2024	None
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	IV	06/28/2024	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
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	M-82	02/16/2024	LABELING REVISIONS RELATED TO CLINICAL STUDIES	Omits this information	02/18/2022	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:		
Notes from previous cycles:		

- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]
- (b)(4)
- M82/S-018- focus on 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:
 - [Redacted]
 - (b)(4)
 - 8/25/2022 assessment- As of 2/18/2022 all patents and exclusivities have been addressed.
 - [Redacted]
 - (b)(4)

[Redacted]

(b)(4)

C6-7/2/2024 Assessment-

[Redacted]

(b)(4)

Deficiency Comments:

4.4 UNITED STATES PHARMACOPEIA (USP) (C6)

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

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

Reviewer Assessment:

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

Reviewer Comments:

None.

Deficiency Comments:

4.5 MODEL CONTAINER LABELS (C6)

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



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

R-03- completed 4/14/2022

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.

OPQ-XOPQ-TEM-0002v01 Page 111 Effective Date: February 1, 2019



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

ANDA Strength	Length (MM)	Imprint Code
24 mg/26 mg	9.5 mm*3.89 mm*3.33 mm	*1272*
49 mg/51 mg	13.18 mm*5.27 mm*3.48 mm	*1273*
97 mg/103 mg	15.24 mm*8.11 mm*5.01 mm	*1274*

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:

An oral suspension dosing was added to the labeling as an alternative administration in 11/24/2019 submission. Firm provided adequate CMC study to support the oral suspension dosing. The assessment of CMC study is located in P2.

Issue Description	Issue Reference Number or Link
N/A	N/A

LABELING LIST OF DEFICIENCIES

Primary Drug Product Assessor Name and Date: Yang Yuan 12/5/2019; 4/24/2020

Secondary Drug Product Assessor Name and Date: Matthew D. Vera, 12/17/2019, 8/11/2020

No labeling issues.

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 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	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. Each film-coated tablet contains following inactive ingredients: colloidal silicon dioxide, crospovidone, hypromellose, low substituted hydroxypropylcellulose, microcrystalline cellulose, polyethylene glycol, sodium stearyl fumarate and titanium dioxide. Additionally, each 49 mg/51 mg tablet contains ferrousferrous oxide, iron oxide red and iron oxide yellow and each 97 mg/103 mg tablet contains FD&C blue #2 Aluminum Lake, FD&C red #40 Aluminum Lake and FD&C yellow #5 (tartrazine) Aluminum Lake. 1/12/23 Assessment- No changes from previous C-4
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. Each film-coated tablet contains following inactive ingredients: colloidal silicon dioxide, crospovidone, hypromellose, low substituted hydroxypropylcellulose, microcrystalline cellulose, polyethylene glycol, sodium stearyl fumarate and titanium dioxide. Additionally, each 49 mg/51 mg tablet contains ferrousferrous oxide, iron oxide red and iron oxide yellow and each 97 mg/103 mg tablet contains FD&C blue #2 Aluminum Lake, FD&C red #40 Aluminum Lake and FD&C yellow #5 (tartrazine) Aluminum Lake. C6- 6/28/2024- No change from previous cycle (5).

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"> <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	1/12/2023 Assessment- no change from previously submitted (C4).																									
Current ANDA Labeling	C6- 6/28/ 2024 Assessment- no change from previously submitted (C5).																									

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)
	Manufactured by: Zydus Lifesciences Limited Ahmedabad, India Distributed by: Zydus Pharmaceuticals (USA) Inc. Pennington, NJ 08534 Rev.: 08/22
Current ANDA Labeling	
Name and Address on ANDA Prescribing Information	(b)(4)
	Manufactured by: Zydus Lifesciences Limited Ahmedabad, India Distributed by: Zydus Pharmaceuticals (USA) Inc. Pennington, NJ 08534 Rev.: 06/24

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

Manufactured by	Manufactured for	Distributed by	Distributed for

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

Reviewer Assessment:

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

Deficiency	No Deficiency	
ESTABLISHED/PROPRIETARY NAME and STRENGTH:		
☐	☒	Tall Man lettering complies with recommendations found on FDA webpage .
☐	☒	Established/proprietary name and strength are the most prominent information on the Principal Display Panel.
☐	☒	No intervening text (written, printed, or graphic matter) between established name and strength.
THE FOLLOWING COMPONENTS ARE PROPERLY DISPLAYED:		
☐	☒	Net quantity statement. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Dosage statement.
☐	☒	NDC number : prominence, linear bar code, and its orientation.
☐	☒	Expiration date and lot number (or placeholder).
☐	☒	Equivalency statement (product strength).
☐	☒	Medication Guide Pharmacist instructions [21 CFR 208.24(d)] .
☐	☒	Controlled Substance Symbol .
☐	☒	Image of drug product represents the true size, color, and imprint.
☐	☒	Yellow #5 (tartrazine) warning statement is properly displayed.
☐	☒	Alcohol is properly listed [21 CFR 201.10(d)(2)] .
☐	☒	Latex warning statement is properly displayed [21 CFR 801.437.] .
☐	☒	Gluten statement is appropriately stated.
PRODUCT DIFFERENTIATION:		
☐	☒	ANDA is the same color as the RLD labels as required (e.g. warfarin, levothyroxine, enoxaparin). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Multiple strengths are differentiated by use of different color or other acceptable means.
☐	☒	Labels of proposed product is differentiated from related products .
STORAGE, DISPENSING, MANUFACTURER, and PACKAGING:		
☐	☒	Storage/dispensing statement is consistent with the How Supplied section of the insert/RLD/USP. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Manufacturer/Distributor/Packager statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)] .
☐	☒	Tamper evident (controlled substances) requirements are met.
☐	☒	Use of child-resistant closure (CRC) or non-CRC is appropriate. Describe container closure , cite source, and any issues in Reviewer Comments below.
OVERALL ASSESSMENT:		
☐	☒	Requirements met for the required label statements (21 CFR 201.15 and 21 CFR 201.100) . Please enter Reviewer/Deficiency Comments if you select Deficiency.
Reviewer Comments: The 06/14/2022 submission is satisfactory in the current cycle (5). Includes the following: tartrazine warning. (b)(4) “Zydus Lifesciences Limited” on all labels and labeling. C6- no new labels submitted. Previous cycle (5) remains satisfactory.		
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:		
The 06/14/2022 submission is satisfactory in the current cycle (5). Includes the following: tartrazine warning. (b)(4) “Zydus Lifesciences Limited” on all labels and labeling.		
C6- 6/28/2024- No new labels submitted. Previous cycle (5) remains satisfactory.		
Deficiency Comments:		

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

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:		
The 06/14/2022 submission is satisfactory in the current cycle (5). Includes the following: tartrazine warning. (b)(4) “Zydus Lifesciences Limited” on all labels and labeling.		
C6- 6/28/2024: No new labels submitted. Previous cycle (5) remains satisfactory.		
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 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:		

Deficiency	No Deficiency	
☐	☒	All submitted labels and labeling are consistent with the HOW SUPPLIED section.
☐	☒	Physical description (e.g. scoring, color, imprint, capsule size, nozzle tip, cap color) of the finished product in the HOW SUPPLIED section are appropriately displayed.
☐	☒	NDC numbers are present.
☐	☒	Drug product is the same color as the RLD's drug product as required (e.g. warfarin, levothyroxine, enoxaparin).
☐	☒	Storage or dispensing statement is acceptable compared to the RLD/USP monograph. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	" Discard unused portion " for single-dose products.
☐	☒	Manufacturer/Distributor/Packager statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].

REGULATORY/OVERALL ASSESSMENT:

☐	☒	STIC requirements addressed appropriately.
☐	☒	Intent to join the Antiretroviral Pregnancy Registry (APR) upon full approval.
☐	☒	Pregnancy registry information is appropriately included/excluded as required for the RLD.
☐	☒	Patent/exclusivity carve out is acceptable. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Dosage form/strength carve out (RLD combined labeling): justification for retaining information for safety/efficacy.
☐	☒	Prescribing information meets formatting requirements [21 CFR 201.57 (PLR) or 21 CFR 201.80 (non-PLR)].
☐	☒	Prescribing Information is the same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8) . Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

(b)(4)

For the Record, Previous cycle assessments:

Response from OND

(b)(4)

(b)(4)

b. ADVERSE REACTIONS, 6.1,

(b)(4)

(b)(4)

(b)(4)

Cycle 5 assessment 1/11/2023, (b)(4) is adequate (b)(4)

Cycle 6 Assessment 6/28/2024: Labeling (b)(4) v3, final on 6/28/2024.

- (b)(4)
- (b)(4)
- (b)(4)
- (b)(4)
- The applicant's labeling differs from the RLD by the addition of section 5.6 Risk of Allergic Reactions Due to Tartrazine in the ANDA product.
- (b)(4)
- The minor editorial revision recommended below are not necessary prior to approval of this submission.
- The proposed labeling submitted 6/11/2024 is adequate (b)(4) and minor editorial post approval comments.

C6 updated on 7/2/2024 Assessment:

(b)(4)

The proposed labeling submitted 6/28/2024 is adequate with minor editorial post approval comments.

Deficiency Comments:

Deficiency # 1

DOSAGE AND ADMINISTRATION, 2.3 Pediatric Heart Failure, Revise first sentence as follows:

Created in C6

(b)(4)

Prescribing Information Response / Assessment:

Deficiency # 2

Created in C6

(b)(4)

Prescribing Information Response / Assessment:

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: C6-6/28/2024 Proposed labeling models the approved labeling (S-025). Satisfactory in the 06/11/2024 submission based on current (b)(4) labeling template V3 on SP. C6 updated on 7/2/2024 Assessment: Proposed labeling submitted 6/28/2024 models the approved labeling (S-025) (b)(4) (b)(4)		
Deficiency Comments: Deficiency # 1 Created in C6 (b)(4) Patient Information Leaflet Response / Assessment:		

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:
Tartrazine and applicable warning statements remain in the labeling. Confirmation by OPQ is not required for this issue.

Deficiency Comments:



Angela
Payne

Digitally signed by Angela Payne
Date: 7/03/2024 08:27:44AM
GUID: 508da70600028ab611d2ba935d5074a6



Burhan
Nour

Digitally signed by Burhan Nour
Date: 7/03/2024 09:26:07AM
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)	213719
Review Number	5
Applicant Name	Zydus Pharmaceuticals (USA) Inc.
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Sacubitril/Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg
Proposed Proprietary Name	N/A
Submission Received Date	June 14, 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 June 14, 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 60s crc and 180s crc count bottles	06/14/2022	Satisfactory
Blister	Final	10s	06/14/2022	Satisfactory
Carton	Final	100s	06/14/2022	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: 06/2022	06/14/2022	Satisfactory
Medication Guide	N/A	N/A		
Patient Information	Final	Revised: 06/2022	06/14/2022	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 ? 1. BPCA template and Use Patent carve out. exp. 4/1/2023

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.

Yes	No	
		(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

Proprietary Name: Entresto

Established Name: sacubitril/valsartan

Description of Supplement:

S-018- Please refer to your supplemental new drug application (sNDA) dated April 20, 2020, received April 20, 2020, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Entresto (sacubitril/valsartan), Film Coated Tablets.

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.

S-013

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**

Drug Name	Active Ingredients	Strength	dosage Form/Route	Marketing Status	TE Code	RLD	RE
ENTREFO	SACUBITRIL; VALSARTAN	24MG/24MG	TABLET/Oral	Prescription	None	Yes	No
ENTREFO	SACUBITRIL; VALSARTAN	48MG/48MG	TABLET/Oral	Prescription	None	Yes	No
ENTREFO	SACUBITRIL; VALSARTAN	96MG/96MG	TABLET/Oral	Prescription	None	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)

OTHER IMPORTANT INFORMATION:

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

(b)(4)

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

Reviewer Assessment:

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

Reviewer Comments:

Proposed ANDA submission models RLD/S-018 (b)(4)

(b)(4)

The Indications and Usage section was discussed internally and with feedback from OND, DLR has modified the Indications and Usage section (two occurrences) as follows:

1. HIGHLIGHTS

(b)(4)

2. FULL PRESCRIBING INFORMATION, INDICATIONS AND USAGE

Revise section 1.1 Adult Heart Failure to read 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)].

Compared to the RLD original text cited here:
NDA 207620/S-018, approved on 2/16/2021

1. INDICATIONS AND USAGE

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)].

NDA 207620/S-013, approved on 10/1/2019

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.

As of 8/25/2022 there are no open labeling supplements for the RLD.
S-022, S-021 (b)(4) are CMC pending supplements.

Deficiency Comments:

4.3 PATENTS AND EXCLUSIVITIES (C5)

The [Orange Book](#) was searched on 01/11/2023

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,	IV	02/18/2022	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
				BY TITRATING UP FROM HALF THE USUALLY RECOMMENDED STARTING DOSE			
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	02/18/2022	Carve-out
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	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			IV	07/08/2019	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	8101659	01/15/2025			IV	07/08/2019	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	8101659*PED	07/15/2025			IV	07/08/2019	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	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			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	IV	07/08/2019	None
24 mg;26 mg, 49 mg;51 mg,	8796331*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
97 mg;103 mg							
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	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			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	IV	07/08/2019	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	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	viii	02/18/2022	Carve-out
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	9937143	08/22/2033	U-3084	TREATMENT OF HEART FAILURE WITH PRESERVED EJECTION FRACTION	viii	02/18/2022	Carve-out

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

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

Strengths	Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	NPP	10/01/2022	NEW PATIENT POPULATION	Omits this information will market prior to the expiration	12/02/2019	Carve-out

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

Strengths	Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact
				of the NPP exclusivity.		
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	NPP PED	04/01/2023	NEW PATIENT POPULATION; PEDIATRIC EXCLUSIVITY	Omits this information will market prior to the expiration of the NPP exclusivity.		Carve-out
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	M-82	02/16/2024	LABELING REVISIONS RELATED TO CLINICAL STUDIES	Omits this information	02/18/2022	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:

Notes:

-
-
-
-
-
-

(b)(4)

(b)(4)

Deficiency Comments:

4.4 UNITED STATES PHARMACOPEIA (USP) (C5)

The [USP](#) was searched on 01/11/2023

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:

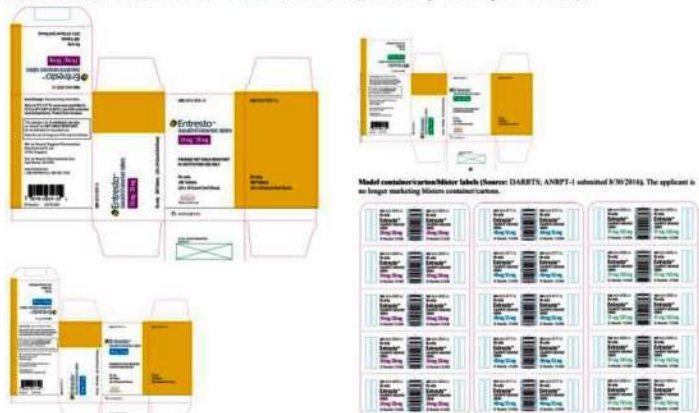
Deficiency	No Deficiency	
☐	☒	Established name is acceptable with regard to the USP monograph or the RLD's nonproprietary name.
☐	☒	RLD's non-proprietary name is different from USP established name.
☐	☒	USP descriptor is correctly used in the appropriate sections of the prescribing information.
USP RECOMMENDATIONS 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: DARRTS; S-016, approved 2/20/2020)



Model container/carton/blister labels (Source: DARTS: ANRPT-3 submitted 8/30/2018). The applicant is delisting and will no longer market the blister pack.



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

R-02- completed 4/2021

R REGIONAL INFORMATION

1.14 Labeling

Labeling & Prescribing Information

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

Is the information accurate? Yes No
If "No," explain.

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

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

Yes No Statement not needed

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

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

i) Is the information accurate? Yes No
If "No," explain.

ii) Are the storage conditions acceptable? Yes No
If "No," explain.

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

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

If "No," explain.



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

ANDA Strength	Length (MM)	Imprint Code
24 mg/26 mg	9.5 mm*3.89 mm*3.33 mm	*1272*
49 mg/51 mg	13.18 mm*5.27 mm*3.48 mm	*1273*
97 mg/103 mg	15.24 mm*8.11 mm*5.01 mm	*1274*

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:

An oral suspension dosing was added to the labeling as an alternative administration in 11/24/2019 submission. Firm provided adequate CMC study to support the oral suspension dosing. The assessment of CMC study is located in P2.

Issue Description	Issue Reference Number or Link
N/A	N/A

LABELING LIST OF DEFICIENCIES

Primary Drug Product Assessor Name and Date: Yang Yuan 12/5/2019; 4/24/2020

Secondary Drug Product Assessor Name and Date: Matthew D. Vera, 12/17/2019, 8/11/2020

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 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	11. DESCRIPTION Sacubitril and valsartan tablets are a combination of sacubitril, a neprilysin inhibitor, and valsartan, an angiotensin II receptor blocker. Sacubitril and valsartan tablets contain a complex comprised of anionic forms of sacubitril and valsartan, sodium cations, and water molecules in the molar ratio of 1:1:3:3, respectively. Following oral administration, the complex dissociates into sacubitril (which is further metabolized to LBQ657) and valsartan. The complex is chemically described as Trisodium [3-((1S,3R)-1-biphenyl-4-yl methyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3-methyl-2-(pentanoyl{2-(tetrazol-5-ylate)biphenyl-4-ylmethyl} amino)butyrate] trihydrate. Its molecular formula (trihydrate) is C₄₈H₅₅N₆O₈Na₃ 3H₂O. Its molecular mass is 967 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. Each film-coated tablet contains following inactive ingredients: colloidal silicon dioxide, crospovidone, hypromellose, low substituted hydroxypropylcellulose, microcrystalline cellulose, polyethylene glycol, sodium stearyl fumarate and titanium dioxide. Additionally, each 49 mg/51 mg tablet contains ferrosferic oxide, iron oxide red and iron oxide yellow and each 97 mg/103 mg tablet contains FD&C blue #2 Aluminum Lake, FD&C red #40 Aluminum Lake and FD&C yellow #5 (tartrazine) Aluminum Lake.
Current ANDA Labeling	11. DESCRIPTION Sacubitril and valsartan tablets are a combination of sacubitril, a neprilysin inhibitor, and valsartan, an angiotensin II receptor blocker. Sacubitril and valsartan tablets contain a complex comprised of anionic forms of sacubitril and valsartan, sodium cations, and water molecules in the molar ratio of 1:1:3:3, respectively. Following oral administration, the complex dissociates into sacubitril (which is further metabolized to LBQ657) and valsartan. The complex

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

	is chemically described as Trisodium [3-((1S,3R)-1-biphenyl-4-yl methyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3-methyl-2-(pentanoyl{2-(tetrazol-5-ylate)biphenyl-4-ylmethyl} amino)butyrate] trihydrate. Its molecular formula (trihydrate) is C₄₈H₅₅N₆O₈Na₃ 3H₂O. Its molecular mass is 967 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. Each film-coated tablet contains following inactive ingredients: colloidal silicon dioxide, crospovidone, hypromellose, low substituted hydroxypropylcellulose, microcrystalline cellulose, polyethylene glycol, sodium stearyl fumarate and titanium dioxide. Additionally, each 49 mg/51 mg tablet contains ferrousferrous oxide, iron oxide red and iron oxide yellow and each 97 mg/103 mg tablet contains FD&C blue #2 Aluminum Lake, FD&C red #40 Aluminum Lake and FD&C yellow #5 (tartrazine) Aluminum Lake. 1/12/23 Assessment- No changes from previously submitted (C4)

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 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 1010 1000 1199"> <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	HOW SUPPLIED/STORAGE AND HANDLING Sacubitril and valsartan tablets 24 mg/26 mg, (sacubitril 24 mg and valsartan 26 mg) are white to off-white colored, film-coated, oval shaped tablets debossed with “” on one side and plain on the other side and are supplied as follows: NDC 70710-1272-6 in bottles of 60 tablets with child-resistant closure NDC 70710-1272-8 in bottles of 180 tablets with child-resistant closure NDC 70710-1272-4 in unit-dose blister cartons of 100 tablets (10 x 10 unit-dose) Sacubitril and valsartan tablets 49 mg/51 mg, (sacubitril 49 mg and valsartan 51 mg) are brown to dark-brown colored, film-coated, oval shaped tablets debossed with “” on one side and plain on the other side and are supplied as follows: NDC 70710-1273-6 in bottles of 60 tablets with child-resistant closure NDC 70710-1273-8 in bottles of 180 tablets with child-resistant closure NDC 70710-1273-4 in unit-dose blister cartons of 100 tablets (10 x 10 unit-dose) Sacubitril and valsartan tablets 97 mg/103 mg, (sacubitril 97 mg and valsartan 103 mg) are light orange to orange colored, film-coated, oval shaped tablets debossed with “” on one side and plain on the other side and are supplied as follows: NDC 70710-1274-6 in bottles of 60 tablets with child-resistant closure NDC 70710-1274-8 in bottles of 180 tablets with child-resistant closure NDC 70710-1274-4 in unit-dose blister cartons of 100 tablets (10 x 10 unit-dose)																									

Table 8: Comparison of Model Labeling to ANDA Labeling	
	Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from moisture.
Current ANDA Labeling	1/12/2023 Assessment- no change from previously submitted (C4).

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) Manufactured by: Zydus Lifesciences Limited Ahmedabad, India Distributed by: Zydus Pharmaceuticals (USA) Inc. Pennington, NJ 08534 Rev.: 08/22

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements			
Manufactured by	Manufactured for	Distributed by	Distributed for
		Distributed by: Zydus Pharmaceuticals (USA) Inc. Pennington, NJ 08534 Rev.: 02/22	

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.

Deficiency	No Deficiency	
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)].
☐	☒	<u>Controlled Substance Symbol</u> .
☐	☒	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)].
☐	☒	<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:		
The 06/14/2022 submission is satisfactory in the current cycle (5). Includes the following: tartrazine warning.		
(b)(4)		
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:		
The 06/14/2022 submission is satisfactory in the current cycle (5). Includes the following: tartrazine warning.		
(b)(4)		
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: The 06/14/2022 submission is satisfactory in the current cycle (5). Includes the following: tartrazine warning.		
(b)(4)		
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.
☐	☒	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.

Deficiency	No 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)

A. HIGHLIGHTS,

(b)(4)

(b)(4)

(b)(4)

B. FULL PRESCRIBING INFORMATION, INDICATIONS AND USAGE, Revise section 1.1 Adult Heart Failure to read 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)].

(b)(4)

(b)(4)

Cycle 5 assessment 1/11/2023, (b)(4) is adequate pending final CP decision.

Deficiency Comments:

Deficiency # 1

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

Created in C4

Prescribing Information

(b)(4)

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

Response / Assessment:

Satisfactory-Addressed in the 6/14/2022 (b)(4)

Deficiency # 2

ADVERSE REACTIONS, Clinical Trials Experience, section 6.1

Created in C4

Prescribing Information

(b)(4)

Response / Assessment:

Satisfactory-Addressed in the 6/14/2022 submission.

Deficiency # 3

Created in C4

General Comments

(b)(4)

(b)(4)

Response / Assessment:

Satisfactory-Addressed in the 6/14/2022 submission.

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: Proposed labeling models the approved labeling (S-018) and provides for NPP carve-outs and P/E carve-out. Satisfactory in the 06/14/2022 submission based on current P/E carve-out template on SP pending final version on CP issues.		
Deficiency Comments: Deficiency # 1 Created in C4 Patient Information Leaflet		
Revise the "What are sacubitril and valsartan tablets?" section to read as follows: 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 Tablets work better when the heart cannot pump a normal amount of blood to the body. It is not known if sacubitril and valsartan tablets is safe and effective in children under 1 year of age.		
Response / Assessment: Addressed in the 06/14/2022 submission to align with the BPCA template.		

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:

Tartrazine and applicable warning statements remain in the labeling. Confirmation by OPQ is not required for this issue.

Deficiency Comments:



Angela
Payne

Digitally signed by Angela Payne

Date: 1/12/2023 09:31:47AM

GUID: 508da70600028ab611d2ba935d5074a6



Burhan
Nour

Digitally signed by Burhan Nour

Date: 1/24/2023 08:45:05PM

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	03/16/2022
ANDA Number(s)	213719
Review Number	4
Applicant Name	Zydus Pharmaceuticals (USA) Inc.
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Sacubitril/Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg
Proposed Proprietary Name	N/A
Submission Received Date	February 18, 2022
Primary Labeling Reviewer	Angela Payne
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 *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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<u>5.1.3</u>	<u>HOW SUPPLIED/STORAGE AND HANDLING</u>
<u>5.1.4</u>	<u>MANUFACTURER, DISTRIBUTOR, AND/OR PACKER</u>
<u>5.2</u>	<u>CONTAINER LABEL (FOR BLISTERS GO TO UNIT-DOSE BLISTERS)</u>
<u>5.2.1</u>	<u>UNIT-DOSE BLISTERS</u>
<u>5.3</u>	<u>CARTON (OUTER OR SECONDARY PACKAGING) LABELING</u>
<u>5.4</u>	<u>PRESCRIBING INFORMATION</u>
<u>5.5</u>	<u>OTHER PATIENT LABELING</u>
<u>6</u>	<u>COMMENTS/CONSULTS FOR OTHER DISCIPLINES</u>

1 LABELING COMMENTS (C4)

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

Labeling deficiencies based on your submission received February 18, 2022:

1. GENERAL COMMENTS

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

2. PRESCRIBING INFORMATION

a. INDICATIONS AND USAGE, Revise Section 1.1 Adult Heart Failure as follows:

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

b. ADVERSE REACTIONS, Clinical Trials Experience, section 6.1

	"A total of 6,622...at least 1 year."

3. PATIENT INFORMATION LEAFLET

Revise the "What are sacubitril and valsartan tablets?" section to read as follows:

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 Tablets work better when the heart cannot pump a normal amount of blood to the body.

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

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.



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 60s crc and 180s crc count bottles	12/2/2019	Satisfactory
Blister	Final	10s	12/2/2019	Satisfactory
Carton	Final	100s	12/2/2019	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	Draft	02/2022	2/18/2022	Revise
Medication Guide	N/A	N/A		
Patient Information	Draft	02/2022	2/18/2022	Revise
Instructions for Use	N/A	N/A		
SPL Data Elements				

4 LABELING REVIEW INFORMATION(C4)

4.1 REGULATORY INFORMATION (C4)

Yes	No	
☒	☐	Are there any applicable issues in DLR's SharePoint Drug Facts ? BPCA template and Use Patent carve out.

DELETED PAGES INFORMATION SHEET

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

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

(b) (4)

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

(b)(4)

4.2 **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

Supplement Approval Date: 02/16/2021

Proprietary Name: Entresto

Established Name: sacubitril/valsartan

Description of Supplement:

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

S-018- Please refer to your supplemental new drug application (sNDA) dated April 20, 2020, received April 20, 2020, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Entresto (sacubitril/valsartan), Film Coated Tablets.
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.

Drug Name	Active Ingredient	Strength	Dosage Form/Route	Marketing Status	TE Code	RLD	RE
ENTRESTO	SACUBITRIL, VALSARTAN	24MG/24MG	TABLET ORAL	Prescription	None	Yes	No
ENTRESTO	SACUBITRIL, VALSARTAN	48MG/48MG	TABLET ORAL	Prescription	None	Yes	No
ENTRESTO	SACUBITRIL, VALSARTAN	87MG/87MG	TABLET ORAL	Prescription	None	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)

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

Reviewer Assessment:

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

Reviewer Comments:

(b)(4)

(b)(4)

4.3 PATENTS AND EXCLUSIVITIES (C4)

The [Orange Book](#) was searched on 03/16/2022

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,	IV	02/18/2022	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
				BY TITRATING UP FROM HALF THE USUALLY RECOMMENDED STARTING DOSE			
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	02/18/2022	Carve-out
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	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			IV	07/08/2019	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	8101659	01/15/2025			IV	07/08/2019	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	8101659*PED	07/15/2025			IV	07/08/2019	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	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			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	IV	07/08/2019	None
24 mg;26 mg, 49 mg;51 mg,	8796331*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
97 mg;103 mg							
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	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			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	IV	07/08/2019	None
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	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	viii	02/18/2022	Carve-out
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	9937143	08/22/2033	U-3084	TREATMENT OF HEART FAILURE WITH PRESERVED EJECTION FRACTION	viii	02/18/2022	Carve-out

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

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

Strengths	Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	NPP	10/01/2022	NEW PATIENT POPULATION	Omits this information will market prior to the expiration	12/02/2019	Carve-out

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

Strengths	Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact
				of the NPP exclusivity.		
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	NPP PED	04/01/2023	NEW PATIENT POPULATION; PEDIATRIC EXCLUSIVITY			
24 mg;26 mg, 49 mg;51 mg, 97 mg;103 mg	M-82	02/16/2024	LABELING REVISIONS RELATED TO CLINICAL STUDIES	Omits this information	02/18/2022	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)

4.4 UNITED STATES PHARMACOPEIA (USP) (C4)

The [USP](#) was searched on 03/16/2022

Table 6: USP

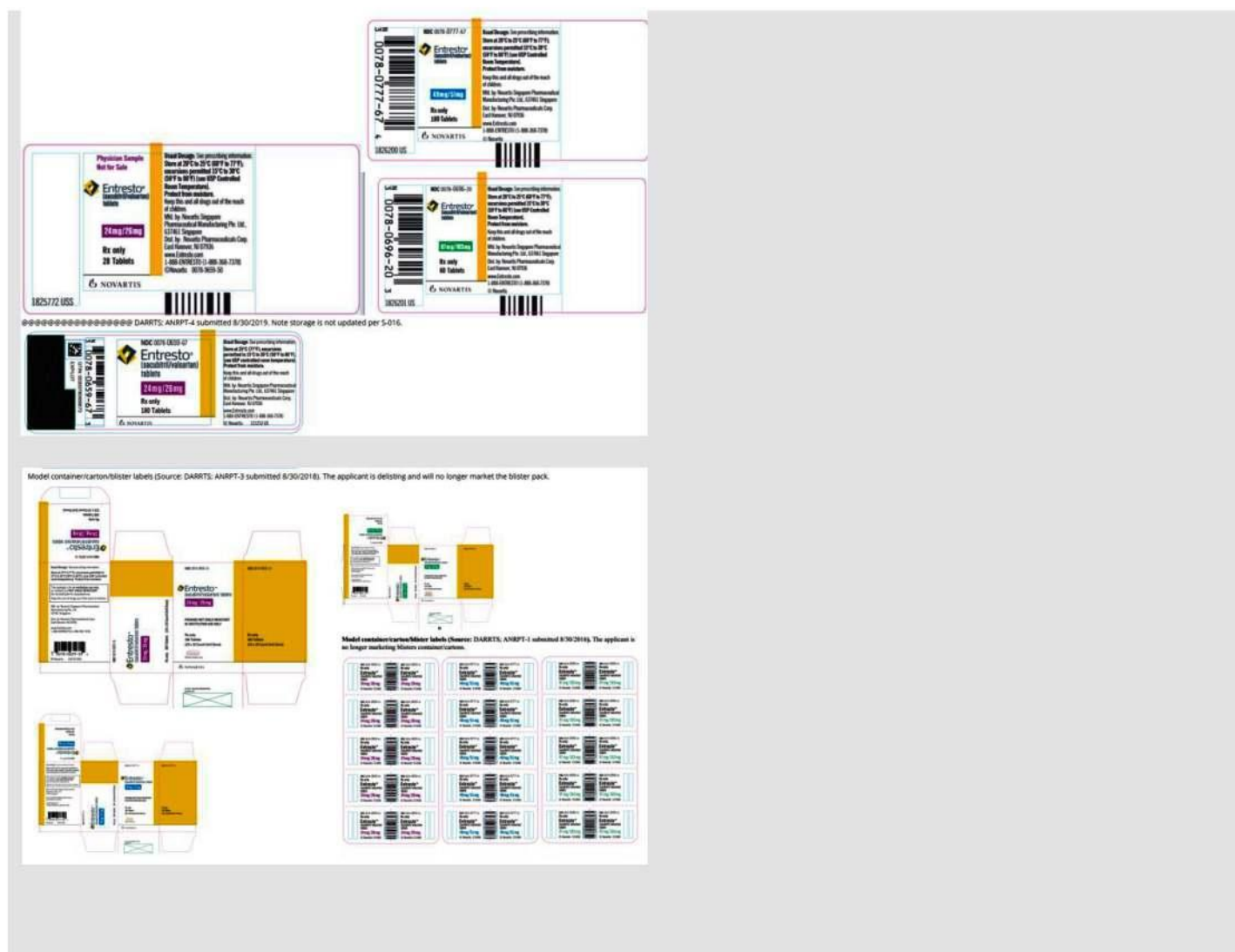
	YES or NO	Date	Monograph Title (N/A if no monograph)	Packaging and Storage/Labeling Statements (N/A if no monograph)
Currently Official	No		N/A	N/A
Not Yet Official	No		N/A	N/A

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 (C4)

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



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

R-02- completed 4/2021

R REGIONAL INFORMATION

1.14 Labeling

Labeling & Prescribing Information

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

Is the information accurate? Yes No
If "No," explain.

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

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

Yes No Statement not needed

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

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

i) Is the information accurate? Yes No
If "No," explain.

ii) Are the storage conditions acceptable? Yes No
If "No," explain.

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

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

If "No," explain.



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

ANDA Strength	Length (MM)	Imprint Code
24 mg/26 mg	9.5 mm*3.89 mm*3.33 mm	*1272*
49 mg/51 mg	13.18 mm*5.27 mm*3.48 mm	*1273*
97 mg/103 mg	15.24 mm*8.11 mm*5.01 mm	*1274*

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:

An oral suspension dosing was added to the labeling as an alternative administration in 11/24/2019 submission. Firm provided adequate CMC study to support the oral suspension dosing. The assessment of CMC study is located in P2.

Issue Description	Issue Reference Number or Link
N/A	N/A

LABELING LIST OF DEFICIENCIES

Primary Drug Product Assessor Name and Date: Yang Yuan 12/5/2019; 4/24/2020

Secondary Drug Product Assessor Name and Date: Matthew D. Vera, 12/17/2019, 8/11/2020

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 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. Each film-coated tablet contains following inactive ingredients: colloidal silicon dioxide, crospovidone, hypromellose, low substituted hydroxypropylcellulose, microcrystalline cellulose, polyethylene glycol, sodium stearyl fumarate and titanium dioxide. Additionally, each 49 mg/51 mg tablet contains ferrosoferric oxide, iron oxide red and iron oxide yellow and each 97 mg/103 mg tablet contains FD&C blue #2 Aluminum Lake, FD&C red #40 Aluminum Lake and FD&C yellow #5 (tartrazine) Aluminum Lake.
Current ANDA Labeling	11. DESCRIPTION Sacubitril and valsartan tablets are a combination of sacubitril, a neprilysin inhibitor, and valsartan, an angiotensin II receptor blocker. Sacubitril and valsartan tablets contain a complex comprised of anionic forms of sacubitril and valsartan, sodium cations, and water molecules in the molar ratio of 1:1:3:3, respectively. Following oral administration, the complex dissociates into sacubitril (which is further metabolized to LBQ657) and valsartan. The complex is chemically described as Trisodium [3-((1S,3R)-1-biphenyl-4-yl methyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3-methyl-2-(pentanoyl{2-(tetrazol-5-ylate)biphenyl-4-ylmethyl} amino)butyrate] trihydrate. Its molecular formula (trihydrate) is C₄₈H₅₅N₆O₈Na₃ 3H₂O. Its molecular mass is 967 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. Each film-coated tablet contains following inactive ingredients: colloidal silicon dioxide, crospovidone, hypromellose, low substituted

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

	hydroxypropylcellulose, microcrystalline cellulose, polyethylene glycol, sodium stearyl fumarate and titanium dioxide. Additionally, each 49 mg/51 mg tablet contains ferrousferic oxide, iron oxide red and iron oxide yellow and each 97 mg/103 mg tablet contains FD&C blue #2 Aluminum Lake, FD&C red #40 Aluminum Lake and FD&C yellow #5 (tartrazine) Aluminum Lake. 3/17/2021 assessment- no changes from previously submitted (C3)

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" data-bbox="483 751 1000 940"> <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	Sacubitril and valsartan tablets 24 mg/26 mg, (sacubitril 24 mg and valsartan 26 mg) are white to off-white colored, film-coated, oval shaped tablets debossed with "1272" on one side and plain on the other side and are supplied as follows: NDC 70710-1272-6 in bottles of 60 tablets with child-resistant closure NDC 70710-1272-8 in bottles of 180 tablets with child-resistant closure NDC 70710-1272-4 in unit-dose blister cartons of 100 tablets (10 x 10 unit-dose) Sacubitril and valsartan tablets 49 mg/51 mg, (sacubitril 49 mg and valsartan 51 mg) are brown to dark-brown colored, film-coated, oval shaped tablets debossed with "1273" on one side and plain on the other side and are supplied as follows: NDC 70710-1273-6 in bottles of 60 tablets with child-resistant closure NDC 70710-1273-8 in bottles of 180 tablets with child-resistant closure NDC 70710-1273-4 in unit-dose blister cartons of 100 tablets (10 x 10 unit-dose) Sacubitril and valsartan tablets 97 mg/103 mg, (sacubitril 97 mg and valsartan 103 mg) are light orange to orange colored, film-coated, oval shaped tablets debossed with "1274" on one side and plain on the other side and are supplied as follows: NDC 70710-1274-6 in bottles of 60 tablets with child-resistant closure NDC 70710-1274-8 in bottles of 180 tablets with child-resistant closure NDC 70710-1274-4 in unit-dose blister cartons of 100 tablets (10 x 10 unit-dose) Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from moisture.																									

Table 8: Comparison of Model Labeling to ANDA Labeling

Current ANDA Labeling	HOW SUPPLIED/STORAGE AND HANDLING Sacubitril and valsartan tablets 24 mg/26 mg, (sacubitril 24 mg and valsartan 26 mg) are white to off-white colored, film-coated, oval shaped tablets debossed with “” on one side and plain on the other side and are supplied as follows: NDC 70710-1272-6 in bottles of 60 tablets with child-resistant closure NDC 70710-1272-8 in bottles of 180 tablets with child-resistant closure NDC 70710-1272-4 in unit-dose blister cartons of 100 tablets (10 x 10 unit-dose) Sacubitril and valsartan tablets 49 mg/51 mg, (sacubitril 49 mg and valsartan 51 mg) are brown to dark-brown colored, film-coated, oval shaped tablets debossed with “” on one side and plain on the other side and are supplied as follows: NDC 70710-1273-6 in bottles of 60 tablets with child-resistant closure NDC 70710-1273-8 in bottles of 180 tablets with child-resistant closure NDC 70710-1273-4 in unit-dose blister cartons of 100 tablets (10 x 10 unit-dose) Sacubitril and valsartan tablets 97 mg/103 mg, (sacubitril 97 mg and valsartan 103 mg) are light orange to orange colored, film-coated, oval shaped tablets debossed with “” on one side and plain on the other side and are supplied as follows: NDC 70710-1274-6 in bottles of 60 tablets with child-resistant closure NDC 70710-1274-8 in bottles of 180 tablets with child-resistant closure NDC 70710-1274-4 in unit-dose blister cartons of 100 tablets (10 x 10 unit-dose) Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from moisture. 3/17/2022 Assessment- no change from previously submitted (C3).

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)		Distributed by: Zydus Pharmaceuticals (USA) Inc. Pennington, NJ 08534 Rev.: 02/22	

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:		
☐	☒	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:		

Found 12/02/2019 submission satisfactory in the previous cycle (3). No new submission since that time. Includes the tartrazine warning.

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:

Found 12/02/2019 submission satisfactory in the previous cycle (3). No new submission since that time. Includes the tartrazine warning.

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:

Found 12/02/2019 submission satisfactory in the previous cycle (3). No new submission since that time. Includes the tartrazine warning.

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)].

Deficiency	No Deficiency	
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:

As of this review cycle (4) submitted 12/3/2021- PI and patient leaflet are inadequate.

(b)(4)

(b)(4)

3/22/2022 Policy

Deficiency Comments:

Deficiency # 1

Created in C4

Prescribing Information

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

(b)(4)

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

Response / Assessment:

Deficiency # 2

ADVERSE REACTIONS, Clinical Trials Experience, section 6.1

Created in C4

(b)(4)

Prescribing Information

(b)(4) A total of 6,622...at least 1 year." (b)(4)

Response / Assessment:

(b)(4)

Deficiency # 3

Created in C4

General Comments

(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:

(b)(4)

Deficiency Comments:

Deficiency # 1

Revise the "What are sacubitril and valsartan tablets?" section to read as follows:

Created in C4

Patient Information Leaflet

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 Tablets work better when the heart cannot pump a normal amount of blood to the body.

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

Response / Assessment:

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:

Deficiency Comments:



Angela
Payne

Digitally signed by Angela Payne
Date: 4/13/2022 12:16:25PM
GUID: 508da70600028ab611d2ba935d5074a6



Burhan
Nour

Digitally signed by Burhan Nour
Date: 4/14/2022 01:23:56PM
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	6/01/2020
ANDA Number(s)	213719
Review Number	3
Applicant Name	Zydus Pharmaceuticals (USA) Inc.
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	April 16, 2020
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

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 April 16, 2020.

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

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

1.3 POST APPROVAL REVISIONS

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

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 March 31, 2020, based on your submission received December 2, 2019:

1. CARTON LABEL- Unit Dose

(b)(4)

2. PRESCRIBING INFORMATION

(b)(4)

- c. HIGHLIGHTS, RECENT MAJOR CHANGES, revise as follows:

(b)(4)

3. PATIENT LEAFLET

See comment 2(a) Prescribing Information, above.

(b)(4)

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. While it is noted, the RLD has two statements on the blister carton labels, the ANDA included as requested the following:

-

(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:

A BPCA template is found on DLR’s SharePoint dated 3/17/2020 based on S-013. This applicant plans to omit the NPP exclusivity. The template will apply to this ANDA.

This ANDA product contains tartrazine and includes the Warning statements on the container and in the insert labeling.

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. BPCA template.

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

If Yes, please explain. Check PAL#06012020

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.

OTHER IMPORTANT INFORMATION:

- SE-018 submitted 4/20/2020 is pending and will impact labeling.
- Supplement 16 (CBE-30 CMC supplement): PENDING; (b)(4)

(b)(4)

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

(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? **NO**

Reviewer Comments:

The proposed ANDA models the RLD S-013 and revised according to the 3/17/2020, BPCA template as the model. The insert and patient leaflet are adequate.

3.3 MODEL CONTAINER LABELS

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



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.
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 (1-888-368-7376)
© Novartis 0078-0777-20 12118 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.
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 (1-888-368-7376)
© 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.
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 (1-888-368-7376)
© Novartis 121257 US

NDC 0078-0696-20

Entresto®
(sacubitril/valsartan)
tablets

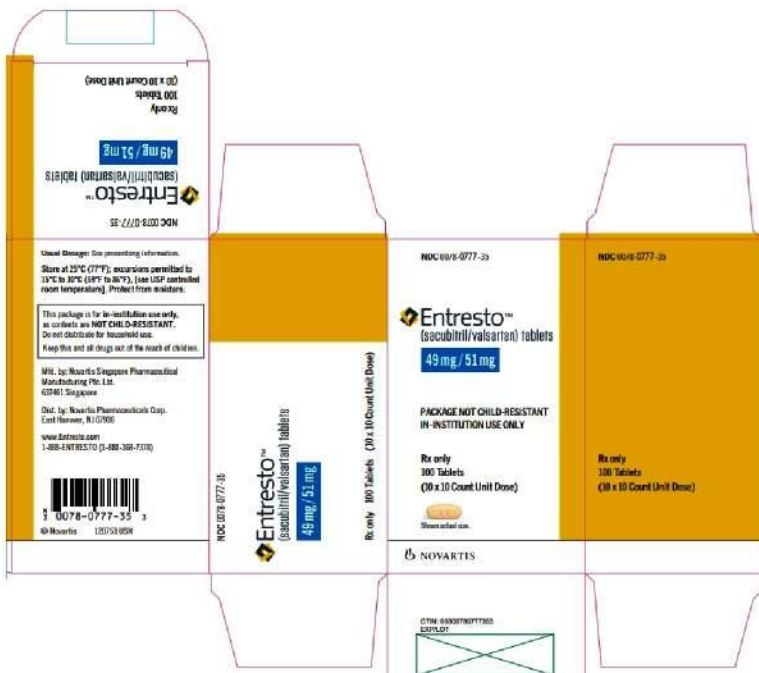
97 mg / 103 mg

Rx only 60 Tablets

NOVARTIS

Usual Dosage: See prescribing information.
Store at 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 (1-888-368-7376)
© 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). The applicant is no longer marketing blisters container/cartons.



3.4 UNITED STATES PHARMACOPEIA (USP)

The USP was searched on 6/1/2020.

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 6/1/2020.

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)

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling

NCE	07/07/2020 PED 01/07/2021	NEW CHEMICAL ENTITY	does not intend to market its proposed 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	Omits this information will market prior to the expiration of the NPP exclusivity.	12/2/2019	Carved out

Reviewer Assessment:

Is the applicant’s “exclusivity carve out” acceptable? **YES**

Reviewer Comments: BPCA template dated 3/17/2020 is the model.

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. Each film-coated tablet contains following inactive ingredients: colloidal silicon dioxide, crospovidone, hypromellose, low substituted hydroxypropylcellulose, microcrystalline cellulose, polyethylene glycol, sodium stearyl fumarate and titanium dioxide. Additionally, each 49 mg/51 mg tablet contains ferrousferic oxide, iron oxide red and iron oxide yellow and each 97 mg/103 mg tablet contains FD&C blue #2 Aluminum Lake, FD&C red #40 Aluminum Lake and FD&C yellow #5 (tartrazine) Aluminum Lake.	(b)(4)

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

Previous Labeling Review	Currently Proposed	Assessment
HOW SUPPLIED/STORAGE AND HANDLING Sacubitril and valsartan tablets 24 mg/26 mg, (sacubitril 24 mg and valsartan 26 mg) are white to off-white colored, film-coated, oval shaped tablets debossed with "" on one side and plain on the other side and are supplied as follows: NDC 70710-1272-6 in bottles of 60 tablets with child-resistant closure NDC 70710-1272-8 in bottles of 180 tablets with child-resistant closure NDC 70710-1272-4 in unit-dose blister cartons of 100 tablets (10 x 10 unit-dose) Sacubitril and valsartan tablets 49 mg/51 mg, (sacubitril 49 mg and valsartan 51 mg) are brown to dark-brown colored, film-coated, oval shaped tablets debossed with "" on one side and plain on the other side and are supplied as follows: NDC 70710-1273-6 in bottles of 60 tablets with child-resistant closure NDC 70710-1273-8 in bottles of 180 tablets with child-resistant closure NDC 70710-1273-4 in unit-dose blister cartons of 100 tablets (10 x 10 unit-dose) S acubitril and valsartan tablets 97 mg/103 mg, (sacubitril 97 mg and valsartan 103 mg) are light orange to orange colored, film-coated, oval shaped tablets debossed with "" on one side and plain on the other side and are supplied as follows: NDC 70710-1274-6 in bottles of 60 tablets with child-resistant closure NDC 70710-1274-8 in bottles of 180 tablets with child-resistant closure NDC 70710-1274-4 in unit-dose blister cartons of 100 tablets (10 x 10 unit-dose) Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from moisture.	Sacubitril and valsartan tablets 24 mg/26 mg, (sacubitril 24 mg and valsartan 26 mg) are white to off-white colored, film-coated, oval shaped tablets debossed with "1272" on one side and plain on the other side and are supplied as follows: NDC 70710-1272-6 in bottles of 60 tablets with child-resistant closure NDC 70710-1272-8 in bottles of 180 tablets with child-resistant closure NDC 70710-1272-4 in unit-dose blister cartons of 100 tablets (10 x 10 unit-dose) Sacubitril and valsartan tablets 49 mg/51 mg, (sacubitril 49 mg and valsartan 51 mg) are brown to dark-brown colored, film-coated, oval shaped tablets debossed with "1273" on one side and plain on the other side and are supplied as follows: NDC 70710-1273-6 in bottles of 60 tablets with child-resistant closure NDC 70710-1273-8 in bottles of 180 tablets with child-resistant closure NDC 70710-1273-4 in unit-dose blister cartons of 100 tablets (10 x 10 unit-dose) Sacubitril and valsartan tablets 97 mg/103 mg, (sacubitril 97 mg and valsartan 103 mg) are light orange to orange colored, film-coated, oval shaped tablets debossed with "1274" on one side and plain on the other side and are supplied as follows: NDC 70710-1274-6 in bottles of 60 tablets with child-resistant closure NDC 70710-1274-8 in bottles of 180 tablets with child-resistant closure NDC 70710-1274-4 in unit-dose blister cartons of 100 tablets (10 x 10 unit-dose) Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F 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
(b)(4)		No changed

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 crc, 60s crc and 180s crc count bottles)	12/2/2019	Satisfactory
Blister	Final	10s	12/2/2019	Satisfactory
Carton	Final	100s	12/2/2019	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	Draft	Revised: 04/2020	4/16/2020	Satisfactory
Medication Guide	NA			
Patient Information	Draft	Revised: 04/2020	4/16/2020	Satisfactory
SPL Data Elements	1 st cycle	Click here to enter text.	Click here to enter text.	Click here to enter text.



Angela
Payne

Digitally signed by Angela Payne

Date: 6/02/2020 09:24:16AM

GUID: 508da70600028ab611d2ba935d5074a6



Theresa
Liu

Digitally signed by Theresa Liu

Date: 6/04/2020 11:14:12AM

GUID: 508da70a00028d58911de18a598cda6f

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	3/31/2020
ANDA Number(s)	213719
Review Number	2
Applicant Name	Zydus Pharmaceuticals (USA) Inc.
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	12/02/2019
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 March 31, 2020, based on your submission received December 2, 2019:

1. CARTON LABEL- Unit Dose

(b)(4)

2. PRESCRIBING INFORMATION

a.

b.

c.

(b)(4)

3. PATIENT LEAFLET

See comment 2(a) Prescribing Information, above.

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

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

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

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are

addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

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

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

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

1.3 POST APPROVAL REVISIONS

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

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:

Previous cycle 1, Labeling Deficiencies determined on October 2, 2019, based on your submission received July 8, 2019:

1. **GENERAL COMMENT-** This drug product contains more than 1 active moiety. Use the word “and” in the established name when cross reference to “Entresto” is made in the reference listed drug labeling. i.e. “sacubitril and valsartan tablets”. We recommend this change to your labels principal display panel and in the insert/patient leaflet labeling. Use title case letter in the product name when appropriate.
2. **CONTAINER LABELS**
 - a. Revise the expression of strength statement by deleting the extra spaces (eq., XX mg/XX mg rather than XX mg / XX mg)
 - b. Relocate the net quantity statement to the bottom portion of the label or top portion near the NDC numbers to ensure this statement is not near the declaration of strength statement.
3. **BLISTER LABELS,** please note comment under CONTAINER LABELS (2.a.) above, regarding the extra space in the strength statement.
4. **UNIT DOSE CARTONS**

(b)(4)

- b. Please refer to CONTAINER LABELS, comment (a) and revise cartons accordingly.
5. **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. **BLACK BOXED WARNING,** revise to read “...discontinue sacubitril and valsartan tablets as soon... [note- add “tablets”]
 - d. Throughout the labeling and especially in the INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, DESCRIPTION, and HOW SUPPLIED sections, please ensure “tablets” is part of the established name wherever “Entresto” is cited in the reference listed drug insert labeling.
 - e. **DESCRIPTION** section declare “tartrazine” in association with FD&C yellow #5 in the description section.
 - f. **WARNING AND PRECAUTIONS**

The 97 mg/103 mg strength tablets contain FD&C Yellow # 5 (tartrazine) aluminum lake. Include the required warning statement to appear as the last subsection in the WARNINGS AND PRECAUTIONS section of the labeling titled "5.X Risk of Allergic Reactions Due to Tartrazine", in accordance with 21 CFR 201.20 (b). Additionally, include the subsection number in the FULL PRESCRIBING INFORMATION: CONTENTS*.

6. PATIENT INFORMATION

a. See comments under professional labeling regarding updates to the RLD labeling.

b. (b)(4)

c. (b)(4)

(b)(4)

3/30/2020 Reviewer's assessment: Applicant responded to the deficiencies from cycle 1. The container, blisters, cartons are adequate. (b)(4)

- (b)(4)

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. While it is noted, the RLD has two statements on the blister carton labels that the ANDA includes or added as requested in the deficiency letter the following was determined after the issuance of the DRL:

- (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:

(b)(4)

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

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

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

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):

- 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.

- 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:

- Under **What should I tell my doctor before taking ENTRESTO?** the following bullet was added:

- have a history of hereditary angioedema

- The **CONTENTS** section was updated to reflect the addition of the new section (6.2).

- 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? **NO**

Reviewer Comments:

The proposed ANDA models the RLD S-013. Some NPP text is retained in the current labeling. The BPCA template will apply to this ANDA. The insert and patient leaflet are inadequate-pending carve-out of NPP per OGD templated emailed to applicants on 3/17/2020.

3.3 MODEL CONTAINER LABELS

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





 N 0078-0659-20

 GTIN: 0030079089238

 EXP/LOT:

 8


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



 N 0078-0777-67

 GTIN: 00300790777674

 EXP/LOT:

 4


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



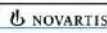
 EXP/LOT:

**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



 N 0078-0777-20

 GTIN: 00300790777209

 EXP/LOT:

 9


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



 N 0078-0696-67

 GTIN: 00300790696678

 EXP/LOT:

 8


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

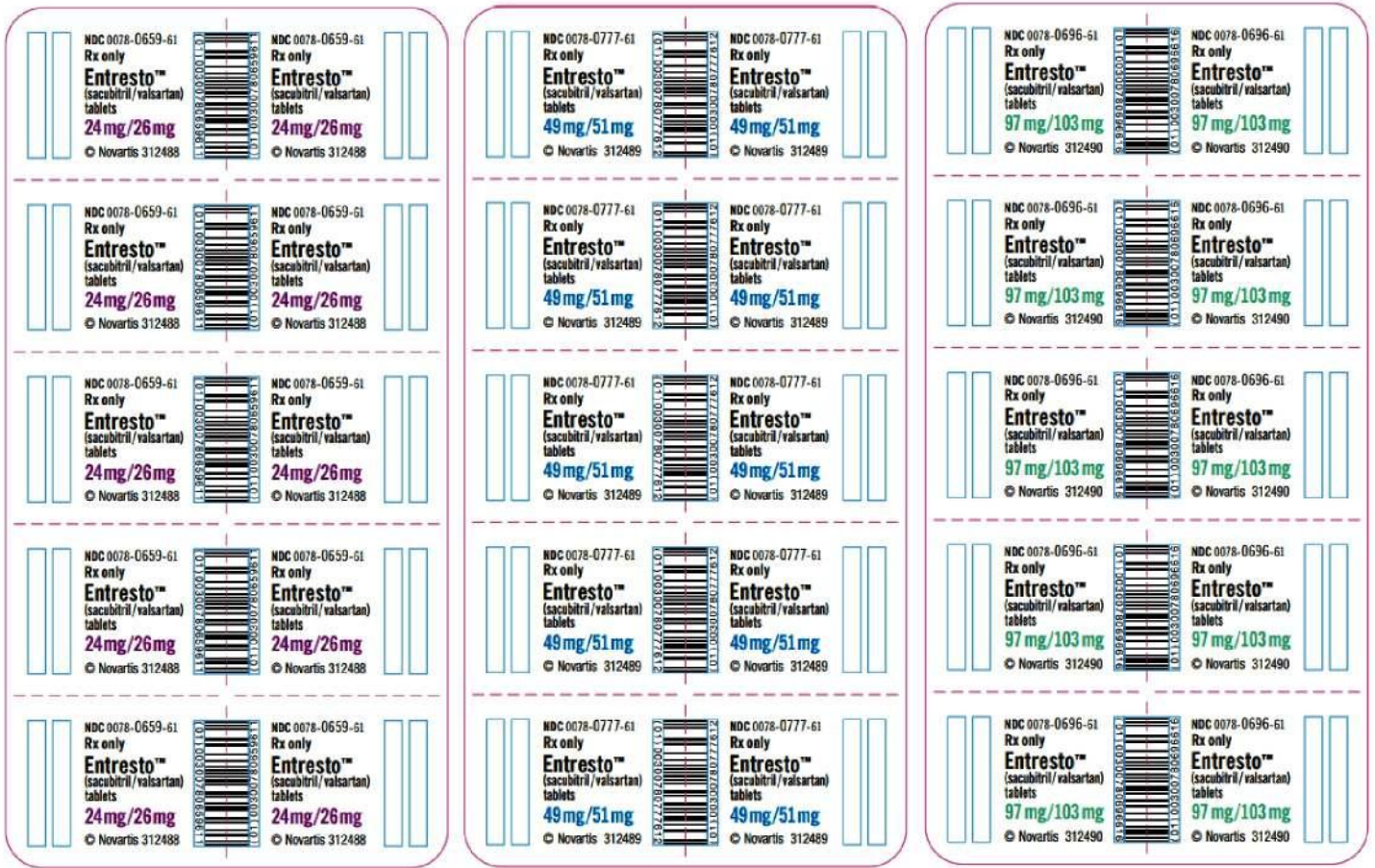


Model container/carton/blister labels (Source: DARRTS; ANRPT-3 submitted 8/30/2018)





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 3/31/2020.

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 3/31/2020.

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 its proposed 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	Omits this information will market prior to the expiration of the NPP exclusivity.	12/2/2019	Carved out

Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **NO**

Reviewer Comments:

The applicant proposed labeling prior to the OGD template issued on 3/17/2020. There are additional changes needed to the proposed applicant's labeling.

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. Each film-coated tablet contains following inactive ingredients: colloidal silicon dioxide, crospovidone, hypromellose, low substituted hydroxypropylcellulose, microcrystalline cellulose, polyethylene glycol, sodium stearyl fumarate and titanium dioxide. Additionally, each 49 mg/51 mg tablet contains ferrousferic oxide, iron oxide red and iron oxide yellow and each 97 mg/103 mg tablet contains FD&C blue #2 Aluminum Lake, FD&C red #40 Aluminum Lake and FD&C yellow #5 (tartrazine) Aluminum Lake.	(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

HOW SUPPLIED/STORAGE AND HANDLING Sacubitril and valsartan tablets 24 mg/26 mg, (sacubitril 24 mg and valsartan 26 mg) are white to off-white colored, film-coated, oval shaped tablets debossed with "" on one side and plain on the other side and are supplied as follows: NDC 70710-1272-6 in bottles of 60 tablets with child-resistant closure NDC 70710-1272-8 in bottles of 180 tablets with child-resistant closure NDC 70710-1272-4 in unit-dose blister cartons of 100 tablets (10 x 10 unit-dose) Sacubitril and valsartan tablets 49 mg/51 mg, (sacubitril 49 mg and valsartan 51 mg) are brown to dark-brown colored, film-coated, oval shaped tablets debossed with "" on one side and plain on the other side and are supplied as follows: NDC 70710-1273-6 in bottles of 60 tablets with child-resistant closure NDC 70710-1273-8 in bottles of 180 tablets with child-resistant closure NDC 70710-1273-4 in unit-dose blister cartons of 100 tablets (10 x 10 unit-dose) S acubitril and valsartan tablets 97 mg/103 mg, (sacubitril 97 mg and valsartan 103 mg) are light orange to orange colored, film-coated, oval shaped tablets debossed with "" on one side and plain on the other side and are supplied as follows: NDC 70710-1274-6 in bottles of 60 tablets with child-resistant closure NDC 70710-1274-8 in bottles of 180 tablets with child-resistant closure NDC 70710-1274-4 in unit-dose blister cartons of 100 tablets (10 x 10 unit-dose) Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from moisture.	Sacubitril and valsartan tablets 24 mg/26 mg, (sacubitril 24 mg and valsartan 26 mg) are white to off-white colored, film-coated, oval shaped tablets debossed with "1272" on one side and plain on the other side and are supplied as follows: NDC 70710-1272-6 in bottles of 60 tablets with child-resistant closure NDC 70710-1272-8 in bottles of 180 tablets with child-resistant closure NDC 70710-1272-4 in unit-dose blister cartons of 100 tablets (10 x 10 unit-dose) Sacubitril and valsartan tablets 49 mg/51 mg, (sacubitril 49 mg and valsartan 51 mg) are brown to dark-brown colored, film-coated, oval shaped tablets debossed with "1273" on one side and plain on the other side and are supplied as follows: NDC 70710-1273-6 in bottles of 60 tablets with child-resistant closure NDC 70710-1273-8 in bottles of 180 tablets with child-resistant closure NDC 70710-1273-4 in unit-dose blister cartons of 100 tablets (10 x 10 unit-dose) Sacubitril and valsartan tablets 97 mg/103 mg, (sacubitril 97 mg and valsartan 103 mg) are light orange to orange colored, film-coated, oval shaped tablets debossed with "1274" on one side and plain on the other side and are supplied as follows: NDC 70710-1274-6 in bottles of 60 tablets with child-resistant closure NDC 70710-1274-8 in bottles of 180 tablets with child-resistant closure NDC 70710-1274-4 in unit-dose blister cartons of 100 tablets (10 x 10 unit-dose) Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F 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
(b)(4)		No changed

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 crc, 60s crc and 180s crc count bottles)	12/2/2019	Satisfactory
Blister	Final	10s	12/2/2019	Satisfactory
Carton	Final	100s	12/2/2019	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	12/02/2019	Revise
Medication Guide	NA			
Patient Information	Final	Revised: 11/2019	12/022019	Revise
SPL Data Elements	1 st cycle	Click here to enter text.	Click here to enter text.	Click here to enter text.



Angela
Payne

Digitally signed by Angela Payne

Date: 4/10/2020 08:35:03AM

GUID: 508da70600028ab611d2ba935d5074a6



Betty
Turner

Digitally signed by Betty Turner

Date: 4/10/2020 08:37:53AM

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	10/2/2019
ANDA Number(s)	213719
Review Number	1
Applicant Name	Zydus Pharmaceuticals (USA) Inc.
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 2, 2019, based on your submission received July 8, 2019:

1. **GENERAL COMMENT-** This drug product contains more than 1 active moiety. Use the word “and” (b)(4) in the established name when cross reference to “Entresto” is made in the reference listed drug labeling. i.e. “sacubitril and valsartan tablets”. We recommend this change to your labels principal display panel and in the insert/patient leaflet labeling. Use title case letter in the product name when appropriate.
2. **CONTAINER LABELS**
 - a. Revise the expression of strength statement by deleting the extra spaces (eq., XX mg/XX mg rather than XX mg / XX mg)
 - b. Relocate the net quantity statement to the bottom portion of the label or top portion near the NDC numbers to ensure this statement is not near the declaration of strength statement.
3. **BLISTER LABELS**, please note comment under CONTAINER LABELS (2.a.) above, regarding the extra space in the strength statement.
4. **UNIT DOSE CARTONS**
 - a.

(b)(4)
 - b. Please refer to CONTAINER LABELS, comment (a) and revise cartons accordingly.
5. **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. **BLACK BOXED WARNING**, revise to read “...discontinue sacubitril and valsartan tablets as soon... (b)(4)
 - d. Throughout the labeling and especially in the INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, DESCRIPTION, and HOW SUPPLIED sections, please ensure “tablets” is part of the established name wherever “Entresto” is cited in the reference listed drug insert labeling.

- e. DESCRIPTION section declare “tartrazine” in association with FD&C yellow #5 in the description section.
- f. WARNING AND PRECAUTIONS

The 97 mg/103 mg strength tablets contain FD&C Yellow # 5 (tartrazine) aluminum lake. Include the required warning statement to appear as the last subsection in the WARNINGS AND PRECAUTIONS section of the labeling titled “5.X Risk of Allergic Reactions Due to Tartrazine”, in accordance with 21 CFR 201.20 (b). Additionally, include the subsection number in the FULL PRESCRIBING INFORMATION: CONTENTS*.

6. PATIENT INFORMATION

- a. See comments under professional labeling regarding updates to the RLD labeling.

- b.
- c.

(b)(4)

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

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

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

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

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

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

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia

– National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

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

1.3 POST APPROVAL REVISIONS

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

[Click here to enter text.](#)

2. LABELING REVIEW INFORMATION

2.1 REGULATORY INFORMATION

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

If YES, please explain.

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

If YES, please explain.

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

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)

**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)

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.
- OTHER (Describe):**

2.2.2 MODEL CONTAINER LABELS

Model container/carton/blister 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

EXP/LOT:

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

NDC 0078-0659-20



Entresto®
(sacubitril/valsartan)
tablets

24 mg / 26 mg

Rx only
60 Tablets

NOVARTIS

EXP/LOT: 3 0078-0659-20 8
GTIN: 0030079069208

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

EXP/LOT: 3 0078-0777-67 4
GTIN: 0030079077674

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

EXP/LOT:

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

EXP/LOT: 3 0078-0777-20 9
GTIN: 0030079077209

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

GTIN: 00300780696678
EXP.LOT

NDC 0078-0696-20

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

GTIN: 00300780696620
EXP.LOT

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

Rx only
100 Tablets
(10 x 10 Count Unit Dose)

24 mg / 26 mg

Entresto[™]
(sacubitril/valsartan) tablets

NDC 0078-0659-35

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.

This package is for in-institution use only; see contents are **NOT CHILD-RESISTANT**. Do not distribute for household use. 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 USH

NDC 0078-0659-35

Entresto[™]
(sacubitril/valsartan) tablets

24 mg / 26 mg

Rx only
100 Tablets
(10 x 10 Count Unit Dose)

Entresto[™]
(sacubitril/valsartan) tablets

24 mg / 26 mg

Rx only
100 Tablets
(10 x 10 Count Unit Dose)

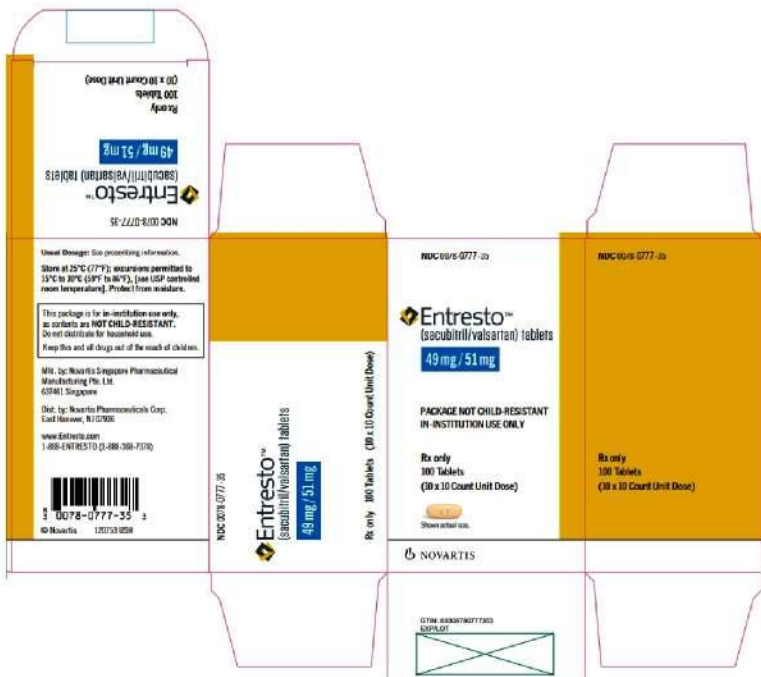
Entresto[™]
(sacubitril/valsartan) tablets

24 mg / 26 mg

Rx only
100 Tablets
(10 x 10 Count Unit Dose)

NOVARTIS

GTIN: 00300780696652
EXP.LOT



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.

	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.)

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

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
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	07/07/2020 PED 01/07/2021	NEW CHEMICAL ENTITY	does not intend to market its proposed prior to the expiration of the NCE exclusivity.	7/8/2019	None
NPP	10/02/2022 PED 04/01/2023	New Patient Population	Will need to address		

2.5 MANUFACTURER, DISTRIBUTOR, AND/OR PACKER

Table 5: Comparison of Manufacturer/Distributor/Packer Labeling Statements		
Name and Address of ANDA Manufacturer/Distributor/Packer (Module 3.2.P.3)	Name and Address on ANDA Container/Carton	Name and Address on ANDA Prescribing Information
(b)(4)		

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.
- The established name is essentially the same as the RLD nonproprietary name. However, this drug product has more than one active moiety. It is noted in the highlight, Title subsection of the RLD labeling "and" is inserted between the names of the two active moieties. (b)(4)
(b)(4) In an effort, to be consistent with the RLD we will ask ANDA to add "tablets" to the established name where the RLD use Entresto in the labeling when not referencing the strength.
- The ANDA proposed product contains tartrazine no.5. the RLD does not. The ANDA has included the tartrazine warning statement in the professional labeling and the Patient leaflet. However, for the this warning is not required in the PL.

21 CFR 201.20 This product contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity." This warning statement shall appear in the "Precautions" section of the labeling.

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	(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? **YES**

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)

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.

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.					
ANDA Labeling	HOW SUPPLIED/STORAGE AND HANDLING Sacubitril and valsartan tablets 24 mg/26 mg, (sacubitril 24 mg and valsartan 26 mg) are white to off-white colored, film-coated, oval shaped tablets debossed with “1272 ” on one side and plain on the other side and are supplied as follows: NDC 70710-1272-6 in bottles of 60 tablets with child-resistant closure NDC 70710-1272-8 in bottles of 180 tablets with child-resistant closure NDC 70710-1272-4 in unit-dose blister cartons of 100 tablets (10 x 10 unit-dose) Sacubitril and valsartan tablets 49 mg/51 mg, (sacubitril 49 mg and valsartan 51 mg) are brown to dark-brown colored, film-coated, oval shaped tablets debossed with “1273 ” on one side and plain on the other side and are supplied as follows: NDC 70710-1273-6 in bottles of 60 tablets with child-resistant closure NDC 70710-1273-8 in bottles of 180 tablets with child-resistant closure NDC 70710-1273-4 in unit-dose blister cartons of 100 tablets (10 x 10 unit-dose) Sacubitril and valsartan tablets 97 mg/103 mg, (sacubitril 97 mg and valsartan 103 mg) are light orange to orange colored, film-coated, oval shaped tablets debossed with “1274 ” on one side and plain on the other side and are supplied as follows: NDC 70710-1274-6 in bottles of 60 tablets with child-resistant closure NDC 70710-1274-8 in bottles of 180 tablets with child-resistant closure NDC 70710-1274-4 in unit-dose blister cartons of 100 tablets (10 x 10 unit-dose) Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F 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 60s, 180s, and UD.

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:

-
-
-

(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? **NO**

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

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

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

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

Is the following information properly displayed?

Net quantity statement: **YES**

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

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

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? **YES**

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:

- The name of the product Sacubitril/Valsartan (b)(4) insert, and patient leaflet. We will recommend use of “and” when the established is used as a title for two active ingredients. See comments under PI above.
- (b)(4)
(b)(4) The generic label declares the presences of tartrazine.
21 CFR 201.20 The label for over-the-counter and prescription drug products intended for human use administered orally, nasally, rectally, or vaginally, or for use in the area of the eye, containing FD&C Yellow No. 5 as a color additive using the names FD&C Yellow No. 5 and tartrazine. The labeling for over-the-counter and prescription drug products shall bear a statement such as “Contains FD&C Yellow No. 5 (tartrazine) as a color additive” or “Contains color additives including FD&C Yellow No. 5 (tartrazine)”.
- It is noted on the container labels for Entresto that an “Each film coated tablet contains...” statement was not included. The ANDA correctly included such statement of ingredients on the side panel.

Containers 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?

Reviewer Comments: We will ask that the “/” symbol be replaced by “and”.
Labels inadequate.

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 Comments:

-
-

(b)(4)

Carton labeling inadequate.

3.2 OTC (OVER THE COUNTER) DRUG PRODUCT

3.2.1 OTC: LABELING THAT INCLUDES DRUGS FACTS INFORMATION

Reviewer Assessment:

Is Drug Facts Labeling format acceptable per [21 CFR 201.66](#)? **CLICK HERE**

Does “Questions?” have a toll-free number no less than 6 pt. font size per [21 CFR 201.66\(c\)\(9\)](#) or “1-800-FDA-1088” per [21 CFR 201.66 \(c\)\(5\)\(vii\)](#)? **CLICK HERE**

Did firm submit a Labeling Format Information Table to evaluate the font size? **CLICK HERE**

Is the applicant’s “patent carve out” acceptable? **CLICK HERE**

Is the applicant’s “exclusivity carve out” acceptable? **CLICK HERE**

Is the established name for this ANDA acceptable? **CLICK HERE**

Is title case used in expressing the established name? **CLICK HERE**

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

Is the following information properly displayed?

Pharmacological category: **CLICK HERE**

Net quantity statement: **CLICK HERE**

Route(s) of administration (other than oral): **CLICK HERE**

Warnings (if any) or cautionary statements (if any): **CLICK HERE**

NDC: **CLICK HERE**

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

Is the Manufacturer/Distributor/Packager statement acceptable? **CLICK HERE**

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

Is the storage statement acceptable? **CLICK HERE**

Does any inactive ingredient require special warnings, precautions, or labeling statements? **CLICK HERE**

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

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

Reviewer Comments:

Click here to enter text.

3.2.1.1 OTC: INACTIVE INGREDIENTS COMPARISON

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

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

Reviewer Assessment:

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

Reviewer Comments:

Click here to enter text.

3.2.1.2 OTC: HOW SUPPLIED AND STORAGE INFORMATION

Table 9: Comparison of Model Labeling to ANDA finished product

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

Reviewer Assessment:

Is the description ([scoring](#), color and [imprint](#)) of the finished product consistent with the Drug Product Quality submission? **CLICK HERE**
Is there any difference in scoring configuration between the ANDA and the Model Labeling? **CLICK HERE**
Are the packaging sizes and configurations acceptable as compared to the Model Labeling? **CLICK HERE**
If the packaging configuration is different than the Model Labeling, does it require addition or deletion of labeling statements? **CLICK HERE**
Is the storage statement acceptable as compared to the Model Labeling? **CLICK HERE**
Is the storage statement acceptable as compared to USP? **CLICK HERE**

Reviewer Comments:

Click here to enter text.

3.2.2 OTC: PATIENT LABELING

Is patient labeling required? **CLICK HERE**

If YES go to Reviewer Assessment below, if NO go to section 3.3.

Reviewer Assessment:

Was patient labeling submitted? **CLICK HERE**

Is the patient labeling the same as the model labeling, except for allowable differences? **CLICK HERE**

Reviewer Comments:

Click here to enter text.

3.3 CONTAINER/CLOSURE

Reviewer Assessment:

Describe container closure (e.g., 30s CRC, 100s non-CRC) and cite source of information in **Reviewer Comments** text box.

Is the use of a child-resistant closure (CRC) or non-CRC appropriate? **YES**

Are the tamper evident requirements met for OTC, Ophthalmic and Controlled Substances **NA**

For ophthalmic products:

Does this ophthalmic product cap color match the American Academy of Ophthalmology (AAO) packaging color-coding scheme? **NA**

For parenteral products:

Is there text on the cap/ferrule overseal of this injectable product? **NA**

If YES, does text comply with the recommendations in USP General Chapter <7> Labeling? **NA**

What is the cap color? **NA**

NOTE: Black closure system is prohibited, except for Potassium Chloride for Injection Concentrate.

(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.

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	No score; 10 mm;1272	See below
49 mg/51 mg	No score; 13 mm; 1273	
97 mg/103 mg	No score; 15 mm;1274	

Reviewer Assessment:

Are the data elements (strength, inactive ingredients, product characteristics, packaging etc.) consistent with the information submitted in the ANDA labeling? **YES**

Reviewer Comments: Module 3.2.P.1

Description of the Drug Product:

Zydus' Sacubitril/Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg which are subject of this ANDA are "immediate-release tablets" with the following description:

Table 1: Description of the drug product

Sacubitril/Valsartan Tablets	
Strength	Product Description
24 mg/26 mg	White to off white colored film coated oval shaped, tablets debossed with "1272" on one side and plain on other side. The tablets should be free of all physical defects.
49 mg/51 mg	Brown to dark brown colored film coated oval shaped, tablets debossed with "1273" on one side and plain on other side. The tablets should be free of all physical defects.
97 mg/103 mg	Light orange to orange colored film coated oval shaped, tablets debossed with "1274" on one side and plain on other side. The tablets should be free of all physical defects.

4. COMMENTS FOR OTHER DISCIPLINES

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

(For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue)

Reviewer Comments: None.

5. SPECIAL CONSIDERATIONS

(b)(4)

6. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Table 12: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	Packaging Sizes	Submission Received Date	Recommendation
Container	Final	24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg (60s and 180s count bottles)	July 8, 2019	Revise
Blister	Final	10s	July 8, 2019	Revise
Carton	Final	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	Draft	Revised 6/2019	July 8, 2019	Revise
Medication Guide	NA			
Patient Information	Draft	Revised: 6/2019	July 8, 2019	Revise
SPL Data Elements	Draft	June 2019	July 8, 2019	Satisfactory



Angela
Payne

Digitally signed by Angela Payne

Date: 11/05/2019 07:33:21AM

GUID: 508da70600028ab611d2ba935d5074a6



Betty
Turner

Digitally signed by Betty Turner

Date: 11/13/2019 04:29:45PM

GUID: 508da70600028acef381be737f7836a9

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 213719

CHEMISTRY REVIEW(s)

ANDA Executive Summary

1. Application/Product Information

ANDA Number.	213719										
Review Cycle #	04										
Applicant Name	ZYDUS PHARMACEUTICALS USA INC										
Drug Product Name	Sacubitril/Valsartan Tablets										
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: 194 mg; Valsartan: 206 mg										
Rx/OTC Dispensed	Rx										
Proposed Indication	(b)(4)										
Drug Product Description	<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr style="background-color: #e6e6fa;"> <th colspan="2" style="text-align: center;">Sacubitril/Valsartan Tablets</th> </tr> <tr style="background-color: #e0ffff;"> <th style="text-align: center;">Strength</th> <th style="text-align: center;">Product Description</th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">24 mg/26 mg</td> <td>White to off white colored film coated oval shaped, tablets debossed with "1272" on one side and plain on other side. (b)(4)</td> </tr> <tr> <td style="text-align: center;">49 mg/51 mg</td> <td>Brown to dark brown colored film coated oval shaped, tablets debossed with "1273" on one side and plain on other side. (b)(4)</td> </tr> <tr> <td style="text-align: center;">97 mg/103 mg</td> <td>Light orange to orange colored film coated oval shaped, tablets debossed with "1274" on one side and plain on other side. (b)(4)</td> </tr> </tbody> </table> (b)(4)	Sacubitril/Valsartan Tablets		Strength	Product Description	24 mg/26 mg	White to off white colored film coated oval shaped, tablets debossed with "1272" on one side and plain on other side. (b)(4)	49 mg/51 mg	Brown to dark brown colored film coated oval shaped, tablets debossed with "1273" on one side and plain on other side. (b)(4)	97 mg/103 mg	Light orange to orange colored film coated oval shaped, tablets debossed with "1274" on one side and plain on other side. (b)(4)
Sacubitril/Valsartan Tablets											
Strength	Product Description										
24 mg/26 mg	White to off white colored film coated oval shaped, tablets debossed with "1272" on one side and plain on other side. (b)(4)										
49 mg/51 mg	Brown to dark brown colored film coated oval shaped, tablets debossed with "1273" on one side and plain on other side. (b)(4)										
97 mg/103 mg	Light orange to orange colored film coated oval shaped, tablets debossed with "1274" on one side and plain on other side. (b)(4)										

	(b)(4)		
Co-packaged product information	N/A		
Device information, if any:	N/A		
Storage Temperature/ Conditions	25°C _± 2 °C/60% _± 5%RH		
Review Team	Discipline	Primary	Secondary
	<i>Drug Substance</i>	Baoqing Ma	Ragine Maheswaran
	<i>Drug Product/ Labeling</i>	Baoqing Ma	Ragine Maheswaran
	<i>Manufacturing</i>	Yeung Chan	Sridhar Thumma
	<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>	Qinghua Ge	
	<i>ATL</i>	Ragine Maheswaran	
Consults	Discipline Consulted	Recommendation	Date
	N/A	N/A	N/A

2. Submission Document(s) Reviewed

Submission(s) Assessed	Documents Date	Disciplines Affected
New application eCTD 0001	07/08/2019	All

Response to IRL eCTD 0002	09/06/2019	Quality
Response to DRL eCTD 0007	02/24/2020	Quality
Response to CRL eCTD 0009	12/28/2020	Quality
Response to CRL eCTD 0010	09/21/2021	Quality
Response to CRL eCTD 0014	06/14/2022	Quality
Response to IRL eCTD 0016	11/14/2022	Quality

3. Related/Supporting Documents

a. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Assessor/Comments
(b)(4)	II	(b)(4)	Sacubitril/Valsartan	Adequate	11/23/22	
	II		(b)(4)	AQAC	11/18/2022	
	III (if applicable)					
	IV (if applicable)					
	Other					

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

Document	Application Number	Description
NDA	207620	RLD Product (Entresto/Novartis)

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.*)

N/A

Drug Substance Deficiencies

N/A

Drug Product Deficiencies

N/A

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

N/A

Manufacturing Deficiencies

N/A

Biopharmaceutics Deficiencies

N/A

Microbiology Deficiencies

N/A

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)*

N/A

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:

In the previous cycle all disciplines are adequate except Facility was on withhold. In this cycle Facility is adequate. DMFs remain adequate.

b. Recommendation by Subdiscipline:

Drug Substance: ADEQUATE

Drug Product: ADEQUATE

Quality Labeling: ADEQUATE

Manufacturing: ADEQUATE

Biopharmaceutics: ADEQUATE

Microbiology: N/A

Environmental: ADEQUATE

6. Life-Cycle Considerations

**Established Conditions per ICH Q12: No
Comments:**

**Comparability Protocols (PACMP): No
Comments:**

Additional Comments: N/A



Ragine
Maheswaran

Digitally signed by Ragine Maheswaran
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CHAPTER I: DRUG SUBSTANCE

[IQA ANDA Assessment Guide Reference](#)

Drug Substance Name	Sacubitril/Valsartan Tablets	
ANDA Number	213719	
Applicant Name	ZYDUS PHARMACEUTICALS USA INC	
Assessment Cycle Number	3	
DMF Number (If Applicable)	(b)(4)	
DMF Status	Adequate	
DMF Status Date		
DMF Holder	(b)(4)	

Assessment Recommendation: Adequate

Theme:

☐ N/A	☐ Other (Requires Division Director Approval)
☐ DMF	☐ Due to Consult
☐ New DS Batch	

Justification: view justification statements found at: [Justification Statements](#)

Paste appropriate justification statement(s) here or insert "N/A" if not applicable.
Other (Requires Division Director Approval)- Assessor writes justification here if "other" selected as theme.

Assessment Summary:

Note:

Drug substance has no USP monograph. **DMF: (b)(4) is adequate on 04/08/2022.**
 Drug product has no USP monograph.
 Drug substance and drug product have no comparability protocol or commitment. ICH Q3D information is satisfactory; Compliance statement included in specifications.

List Submissions being assessed (Table):

Document(s) Assessed	Date Received
Multiple Categories/Subcategories	9/21/2021
Multiple Categories/Subcategories	2/18/2022
Multiple Categories/Subcategories	2/24/2022

Multiple Categories/Subcategories	4/08/2022

List Submissions assessed (Table):

Document(s) Assessed	Date Received
Multiple Categories/Subcategories	12/28/2020
Amendment Correspondence/Amendment Verification Statement; Quality/Response to Discipline Review Letter	02/24/2020
Bioequivalence/Response to Discipline Review Letter; Amendment Correspondence/Amendment Verification Statement	01/09/2020
Quality/Facility Information; Amendment Correspondence/Amendment Verification Statement; Quality/Response To Information Request	09/06/2019
New/ANDA; Form 3674; User Fee/Coversheet	07/07/2019

Highlight Key Issues from Last Cycle and Their Resolution:

DMF is inadequate.

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

None

Select Number of Approved Comparability Protocols: 0

S.1 GENERAL INFORMATION

Summary of the Information

Drug Substance : Sacubitril/Valsartan

USAN : Sacubitril and Valsartan

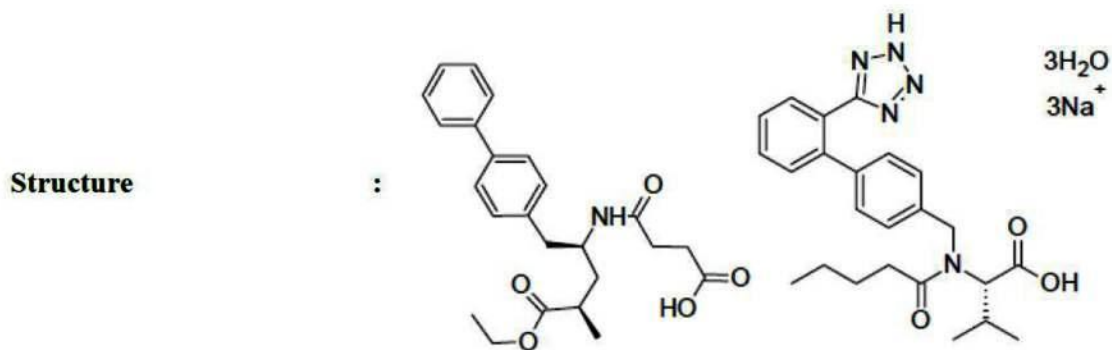
**Chemical Name/
IUPAC Name** : Trisodium [3-((1S,3R)-1-biphenyl-4-yl methyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3-methyl-2-(pentanoyl {2-(tetrazol-5-ylate)biphenyl-4-ylmethyl} amino)butyrate] trihydrate.

Synonyms : Sacubitril and Valsartan trisodium trihydrate

International Non-proprietary Name (INN) : Sacubitril/Valsartan

CAS Registry No. : 936623-90-4

Therapeutic category : Angiotensin receptor neprilysin inhibitor



Molecular Formula : $\text{C}_{48}\text{H}_{55}\text{N}_6\text{Na}_3\text{O}_8 \cdot 3\text{H}_2\text{O}$

Molecular Weight : 967

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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

No comparability protocols were submitted.

Lifecycle Management Considerations

N/A.

DRUG SUBSTANCE LIST OF DEFICIENCIES

None

Primary Drug Substance Assessor Name and Date: Yang Yuan 11/24/2019; 3/23/2020; 4/16/2020.

Baoqing Ma, 7/26/2021 (12/28/2020 amendment), 4/13/2022.

Secondary Assessor Name and Date (and Secondary Summary, as needed): Matthew D. Vera, 12/13/2019; 4/22/2020, 6/11/2020.

Ragine Maheswaran, 7/26/2021 (12/28/2020 amendment), 4/13/2022.

CHAPTER II: DRUG PRODUCT

[IQA ANDA Assessment Guide Reference](#)

Product Information	Sacubitril/Valsartan Tablets
ANDA Number	213719
Assessment Cycle Number	2
Drug Product (DP) Name / Strength	Sacubitril/Valsartan Tablets 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg
Route of Administration	Oral
Drug Product Manufacturer	ZYDUS PHARMACEUTICALS USA INC
RLD/RS Information (Brand Name of Product, Applicant)	ENTRESTO® tablets
RLD/RS Number	N207620
Proposed Indication	(b)(4)

Assessment Recommendation: **Adequate**

Theme:

☐ N/A	☐ Unacceptable Analytical Methods
☐ Unqualified Impurity	☐ Application Quality
☐ New DP Batch	☐ Pharmaceutical Equivalence
☐ Product Design	☐ Product Safety
☐ Failing Stability Data	☐ Other (Requires Division Director Approval)
☐ Application Completeness	☐ Due to Consult

Justification: view justification statements found at: **[Justification Statements](#)**

Paste appropriate justification statement(s) here or insert "N/A" if not applicable.
Other (Requires Division Director Approval)- Assessor writes justification here if "other" selected as theme.

Assessment Summary:

Table 1. ANDA 213719/ Sacubitril/Valsartan Tablets

Drug Product CQAs	FMEC A RPN	Comment	Updated Risk Ranking after Review Cycle #1	Comments*
Physical stability (solid state)	12	(b)(4)	low	(b)(4)
Chemical Stability	24		low	
Assay	18		low	
Content uniformity	12		low	
Microbial limits	9		Low	
Dissolution	12		Low	

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Multiple Categories/Subcategories	12/28/2020
Amendment Correspondence/Amendment Verification Statement; Quality/Response to Discipline Review Letter	02/24/2020
Bioequivalence/Response to Discipline Review Letter; Amendment Correspondence/Amendment Verification Statement	01/09/2020
Quality/Facility Information; Amendment Correspondence/Amendment Verification Statement; Quality/Response To Information Request	09/06/2019
New/ANDA; Form 3674; User Fee/Coversheet	07/07/2019

Highlight Key Issues from Last Cycle and Their Resolution:

Concise Description of Outstanding Issues (*List Bullet Points with Key Information and Update as Needed*):

Select Number of Approved Comparability Protocols: 0

List Current Quality Endorsement Status:

- *USP monograph for Drug Product and compliance (current USP) – status: N/A.*
- *Dissolution status: specifications **are**/are not finalized with Biopharmaceutics, and implemented, and stability data complies with revised specifications (if applicable) to confirm shelf life proposal: Adequate.*
- *Elemental impurity compliance with ICH Q3D – status: Adequate.*
- *Number of Comparability protocols included: __0__*

P.1 DESCRIPTION AND COMPOSITION

Table 1: Description of the drug product

Sacubitril/Valsartan Tablets	
Strength	Product Description
24 mg/26 mg	White to off white colored film coated oval shaped, tablets debossed with “1272” on one side and plain on other side. (b)(4) (b)(4)
49 mg/51 mg	Brown to dark brown colored film coated oval shaped, tablets debossed with “1273” on one side and plain on other side. (b)(4) (b)(4)
97 mg/103 mg	Light orange to orange colored film coated oval shaped, tablets debossed with “1274” on one side and plain on other side. (b)(4) (b)(4)

Table 2: Photograph of test and RLD drug products for Sacubitril/Valsartan Tablets, 24 mg/26 mg

	Proposed Generic Product by Zydus [Sacubitril/Valsartan Tablets 24 mg/26 mg]	Reference Drug Product by Novartis Pharmaceuticals Corp [ENTRESTO® (sacubitril and valsartan) tablets, 24 mg/26 mg]
Identification Mark	White to off white colored film coated oval shaped, tablets debossed with "1272" on one side and plain on other side. (b)(4)	Violet white, unscored, ovaloid, biconvex, film-coated tablets, debossed with "NVR" on one side, and "LZ" on the other side
Visual Image	(b)(4)	

Table 3: Photograph of test and RLD drug products for Sacubitril/Valsartan Tablets, 49 mg/51 mg

	Proposed Generic Product by Zydus [Sacubitril/Valsartan Tablets, 49 mg/51 mg]	Reference Drug Product by Novartis Pharmaceuticals Corp [ENTRESTO® (sacubitril and valsartan) tablets, 49 mg/51 mg]
Identification Mark	Brown to dark brown colored film coated oval shaped, tablets debossed with “1273” on one side and plain on other side. (b)(4) (b)(4)	Pale yellow, unscored, ovaloid, biconvex, film-coated tablets, debossed with “NVR” on one side, and “L1” on the other side.
Visual Image	(b)(4)	

Table 4: Photograph of test and RLD drug products for Sacubitril/Valsartan Tablets, 97 mg/103 mg

	Proposed Generic Product by Zydus [Sacubitril/Valsartan Tablets, 97 mg/103 mg]	Reference Drug Product by Novartis Pharmaceuticals Corp [ENTRESTO® (sacubitril and valsartan) tablets, 97 mg/103 mg]
Identification Mark	Light orange to orange colored film coated oval shaped, tablets debossed with “1274” on one side and plain on other side. (b)(4) (b)(4)	Light pink, unscored, ovaloid, biconvex, film-coated tablets, debossed with “NVR” on one side, and “L11” on the other side.
Visual Image	(b)(4)	

Table 5: Size, Shape and Volume Comparison of the test and RLD drug products

Sr. No	Strength	Size and shape comparison				Volume comparison (mm ³)**		
		Dimension	Reference Product	Test Product	% difference in dimension	Reference Product	Test Product	% difference in Volume
1	24 mg/ 26 mg	Shape	Oval	Oval	NA	(b)(4)		
		Length (mm)	13.27	9.5	- 28.41%			
		Width (mm)	5.28	3.89	-26.33%			
		Thickness (mm)	3.64	3.33	- 8.52%			
2	49 mg/51 mg	Shape	Oval	Oval	NA			
		Length (mm)	13.24	13.18	+ 0.45%			
		Width (mm)	5.27	5.27	0.00%			
		Thickness (mm)	3.72	3.48	- 6.45%			
3	97 mg/103 mg	Shape	Oval	Oval	NA			
		Length (mm)	15.33	15.24	- 0.59%			
		Width (mm)	6.13	6.11	- 0.33%			
		Thickness (mm)	5.54	5.01	- 9.57%			

Component/Composition Table updated in 2/24/2020 submission (Seq. 0007)

Table 6: Qualitative and Quantitative composition per unit (mg/tablet)

Sr. No.	Name of Ingredient	Quantity per Unit (mg)			%w/w**			Function
		24 mg/26 mg	49 mg/51 mg	97 mg/103 mg	24 mg/26 mg	49 mg/51 mg	97 mg/103 mg	
Sacubitril/Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg								
	Sacubitril/Valsartan* [®]	(b)(4)			(b)(4)			Active ingredient
	Microcrystalline Cellulose NF							
	Low Substituted Hydroxy Propyl Cellulose NF							
	Colloidal Silicon Dioxide, NF							
	Sodium Stearyl Fumarate NF							
	(b)(4)							
	(b)(4)	(b)(4)			(b)(4)			
	Crospovidone NF							
	(b)(4)							
	Total (Core Tablet)	102.400	204.800	390.000				

(b)(4)

Assessment: Adequate.

Sacubitril/Valsartan Tablets 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg, are oral shaped film-coated immediate release tablets. 24 mg/26 mg strength tablets are white to off-white color. 49 mg/51 mg strength tablets are brown to dark brown color. 97 mg/103 mg strength are light orange to orange color.

Sacubitril and valsartan tablets should contain 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 as per product labeling.

Firm provided the composition of the drug product table on page 9 of 16 in the [description and composition of the drug product.](#)

(b)(4)

Firm compared the tablets shape, color, size and thickness of the proposed drug product side by side with RLD drug products. The proposed 49 mg/51 mg and 97 mg/103 mg strength products are similar in size and shape to RLD. The proposed 24 mg/26 mg strength products are similar in shape to RLD, but the size is smaller. Therefore, the tablets size and shape met the requirements of FDA guidance. It is acceptable.

The excipients used are all commonly used compendial excipients. The excipients used in the proposed products are similar to those in RLD.

(b)(4)

(b)(4) Therefore, this product is similar in design to RLD.

Based on MDD of 194 mg of Sacubitril and 206 mg of Valsartan, firm stated none of the excipients exceeded the IIG limit for this route of administration. The assessment was covered in Bioequivalence review.

(b)(4)

Response is adequate.

Information Requested:

1.

(b)(4)

(b)(4)

Reviewer's assessment on 2/24/2020 submission: Adequate.

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Methods Validation or Verification Package

Assessment: Refer to S.5 and P.5.

Comparability Protocols

Assessment: N/A.

No comparability protocols were provided.

Lifecycle Management Considerations

N/A.

DRUG PRODUCT LIST OF DEFICIENCIES

N/A

*Primary Drug Product Assessor Name and Date: Yang Yuan 12/4/2019; 4/2/2020
Baoqing Ma, 7/6/2021 (12/28/2020 amendment).*

*Secondary Assessor Name and Date (and Secondary Summary, as needed):
Matthew D. Vera, 12/16/2019; 4/22/2020, 6/11/2020.*

Ragine Maheswaran, 7/16/2021 (12/28/2020 amendment).

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	Length (MM)	Imprint Code
24 mg/26 mg	9.5 mm*3.89 mm*3.33 mm	"1272"
49 mg/51 mg	13.18 mm*5.27 mm*3.48 mm	"1273"
97 mg/103 mg	15.24 mm*6.11 mm*5.01 mm	"1274"

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:

An oral suspension dosing was added to the labeling as an alternative administration in 11/24/2019 submission. Firm provided adequate CMC study to support the oral suspension dosing. The assessment of CMC study is located in P2.

Issue Description	Issue Reference Number or Link
N/A	N/A

LABELING LIST OF DEFICIENCIES

Primary Drug Product Assessor Name and Date: Yang Yuan 12/5/2019; 4/24/2020

Secondary Drug Product Assessor Name and Date: Matthew D. Vera, 12/17/2019, 6/11/2020



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Maheswaran

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Ma

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MANUFACTURING INTEGRATED ASSESSMENT

Application ID	ANDA 213719
Drug Product Name	Sacubitril/Valsartan Tablets
Strengths	24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg
Dosage Form	Tablet
Administration Route	Oral
Indication	(b)(4)
Applicant Name	Zydus Pharmaceuticals (USA) Inc.
RLD Number	N207620

I. Manufacturing Summary

Facility Assessment Recommendation: Adequate

Process Assessment Recommendation: Adequate

Assessment Summary:

Process: Sacubitril and Valsartan Film-Coated Tablets (Sacubitril and Valsartan Tablets), 24/26 mg, 49/51 mg and 97/103 mg, a generic version of the Entresto® 24/26 mg, 49/51 mg and 97/103 mg. (b)(4)

(b)(4)

(b)(4) All process deficiencies were addressed by the firm's DRL response dated 02/24/2020.

Facility:

Third cycle review: Following a recently completed for-cause cGMP inspection on

(b)(4)
(b)(4)
(b)(4) this DP

site is now acceptable for the proposed manufacturing operations as stated in ANDA 213719.

Overall, ANDA 213719 is recommended for approval from manufacturing perspective per Assessment #3.

First cycle review: Following a review of the inspectional histories (b)(4), a Withhold recommendation is made based on: (b)(4)

(b)(4)

(b)(4)

(b)(4) Therefore, this application is considered to be incomplete and a new (b)(4) facility need to be provided in the next cycle.

Second cycle review: (b)(4)

(b)(4)

List Submissions being assessed (Table):

Document Description (SD #)	Date Received
Original Submission (SD-1)	07/08/2019
IR response (SD-2)	09/06/2019
DRL response (SD-7)	02/24/2020
CR response (SD-9)	12/28/2020
CR response (SD-10)	09/21/2021
CR response (SD-14)	06/14/2022

Highlight Key Issues from Last Cycle and Their Resolution: Second Cycle Review

(b)(4)

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

Facility: *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
(b)(4)			Approve - Based on Previous History

(b)(4)	
	Approve - Based on PAI
	(b)(4)
	Approve - Based on PAI
	Other : Approve based on 704(a)(4) response
*Not for FOIA:	
(b)(4)	

II. (b)(4) Manufacturing

1. Batch Formula

****** Response to DRL (SD-7) ******

Table 4: Batch Formula Details for (b)(4) for Sacubitril/Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg

Sr. No.	Name of Ingredient	Quantity / Unit (mg)			Quantity/Batch (kg)		%w/w
		24 mg/ 26 mg	49 mg/ 51 mg	97 mg/ 103 mg	Exhibit Batch	Intended Batch	
(b)(4)							
1	Sacubitril/Valsartan	(b)(4)			(b)(4)		(b)(4)
2	Microcrystalline Cellulose NF (b)(4)						
3	Low Substituted Hydroxy Propyl Cellulose NF (b)(4)						
4	Colloidal Silicon Dioxide, NF (b)(4)						
5	Sodium Stearyl Fumarate NF (b)(4)						
Total (Core Tablets)		90.250	180.500	361.000			100.00

(b)(4)

**** **Original Submission (SD-1)** ****

Bifurcation of Common granules for Sacubitril/Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg:

Table 2: Bifurcation of Common Granules

Strength	Exhibit Batch (Total: 88.445 Kg)	Intended Batch (Total: 88.445 Kg)
Part A – for Sacubitril/Valsartan Tablets, 97 mg/103 mg	Part: A – 50.540 Kg (≈140,000 Tablets)	Part: A – 50.540 Kg (≈140,000 Tablets)
Part B – for common blend for Sacubitril/Valsartan Tablets 24 mg/26 mg and 49 mg/51 mg	Part: B – 37.905 Kg (≈140,000 Tablets of 24 mg/26 mg and 49 mg/51 mg each)	Part: B – 37.905 Kg (≈140,000 Tablets of 24 mg/26 mg and 49 mg/51 mg each)

Bifurcation of Common blend for Sacubitril/Valsartan Tablets, 24 mg/26 mg and 49 mg/51 mg:

Table 3: Bifurcation of Common Blend

Strength	Exhibit Batch (Total: 43.008 Kg)	Intended Batch (Total: 43.008 Kg)
Part A – for Sacubitril/Valsartan Tablets 24 mg/26 mg	Part: A – 14.336 Kg (≈140,000 Tablets)	Part: A – 14.336 Kg (≈140,000 Tablets)
Part B – for Sacubitril/Valsartan Tablets 49 mg/51 mg	Part: B – 28.672 Kg (≈140,000 Tablets)	Part: B – 28.672 Kg (≈140,000 Tablets)

Table 4: Batch Formula Details for Common granules for Sacubitril/Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg

Sr. No.	Name of Ingredient	Quantity / Unit (mg)			Quantity/Batch (kg)		%w/w
		24 mg/ 26 mg	49 mg/ 51 mg	97 mg/ 103 mg	Exhibit Batch (88.445 Kg)	Intended Batch (88.445 Kg)	
For Common granules							
1	Sacubitril/Valsartan*	54.070	108.140	216.280	52.989\$	52.989\$	59.91
2	Microcrystalline Cellulose NF (Avicel PH101)	31.430	62.860	125.720	30.801@	30.801@	34.83
3	Low Substituted Hydroxy Propyl Cellulose NF (LH-11)	2.500	5.000	10.000	2.450	2.450	2.77
4	Colloidal Silicon Dioxide, NF (Aerosil 200)	1.250	2.500	5.000	1.225	1.225	1.39
5	Sodium Stearyl Fumarate NF	1.000	2.000	4.000	0.980	0.980	1.11
Total (Core Tablets)		90.250	180.500	361.000	88.445	88.445	100.00

\$ The actual quantity of Sacubitril/Valsartan shall be calculated based on Assay on Anhydrous basis and (% w/w) and water by KF (% w/w).

@ The actual quantity of microcrystalline cellulose shall be calculated based on actual quantity of Sacubitril/Valsartan.

* Based on conversion factor considering molecular weight of Sacubitril, Sacubitril sodium, valsartan, valsartan disodium as 411.49, 434.479, 435.519 and 481.497 respectively. (Conversion factor is 1.081424). Given factor does not include compensation for water adduct in active ingredient. Each 90.250 mg common granules contain 24 mg (24.3 mg) of sacubitril and 26 mg (25.7 mg) of valsartan.

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(b)(4)

V. List of Outstanding Information Request/Deficiencies:

Outstanding Deficiencies Collation Table

VI. Signature Block

Round#	Primary Name	Secondary & Other Names	Date of Completion	Assessment Outcome	Facility OMIR
1	Teng Xu, Ph.D.	Vikas Moolchandani, Ph.D.	12/6/2019	IR	TBD
2	Teng Xu, Ph.D.	Vikas Moolchandani, Ph.D.	5/27/2020	CR Major	Withheld

		Jonathan Swoboda, Ph.D.			
3	Yoon Oh	Jonathan Swoboda	1/12/2021	CR Major	Withheld
4	Yeung Chan	Sridhar Thumma	12/21/2022	Adequate	Approve



Yeung
Chan

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Sridhar
Thumma

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BIOPHARMACEUTICS ANDA REVIEW	
Application No.	ANDA-213719-ORIG-1
Applicant	Zydus Pharmaceuticals (USA) Inc.
Product Name/ Strength(s)	Sacubitril/Valsartan Tablets 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg
Dosage Form/Route	Immediate-release tablet/Oral
Indication	Reduce the risk of cardiovascular death and hospitalization for heart failure
Submission Date(s)	7/8/2019 – Original Submission 2/24/2020 – 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 criterion for quality control testing of the proposed drug product.

Dissolution Method and Acceptance Criterion:

(b)(4)

Therefore, in an Information Request dated December 23, 2019, the Applicant was recommended to investigate the discriminating ability of the method (b)(4)

In a Response dated February 24, 2020, the Applicant adopted the new FDA dissolution database method (Table 2) (b)(4)

The Applicant demonstrated discriminatory ability and suitability of the newly proposed dissolution method. Based on the provided information and data, the newly proposed dissolution method and acceptance criterion are acceptable for quality control testing of the proposed drug product.

¹ [FDA Recommended Dissolution Methods](#)

² [Application 213719 - Sequence 0007 - Cover Letter \(0007\) \(02242020\)](#)

Table 1. Originally proposed dissolution method and acceptance criterion by the Applicant³

Method Source	USP Apparatus	Speed	Medium	Volume/ Temperature	Proposed Acceptance Criteria
(b)(4)					

Recommendation:

From a Biopharmaceutics perspective, ANDA 213719 for the proposed Sacubitril/Valsartan Tablets, is **adequate** and recommended for **approval**.

The approved dissolution method and acceptance criterion for the proposed drug product are presented below:

Table 2. Approved dissolution method and acceptance criterion⁵

Method Source	USP Apparatus	Speed	Medium	Volume/ Temperature	Acceptance Criterion [for both Sacubitril and Valsartan]
FDA – Database	I (Basket)	75 RPM	pH 6.8 phosphate buffer	900 mL/ 37°C ± 0.5°C	Q = □% in 30 minutes

³ [Application 213719 - Sequence 0001 - 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods-pdf](#)

⁴ Previous method

⁵ [Application 213719 - Sequence 0007 - Dissolution Development Report](#)

BIOPHARMACEUTICS REVIEW

1. **Drug Substance Solubility:** The Applicant submitted solubility data for Sacubitril and Valsartan, (b)(4)

(b)(4)

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

(b)(4)

3. **Bioequivalence and PK Characteristics:** The Applicant performed *in vivo* pharmacokinetic studies using the 97 mg/103 mg tablets of the proposed and RLD products in both fasting and fed conditions. The Applicant performed another *in vivo* pharmacokinetic study using the lower strength of 24/26 mg tablet of the proposed and RLD product under fasting conditions. Under fasting conditions, the T_{max} of Sacubitril is 0.5 hours and Valsartan is 1.75 hours. Under fed conditions, the T_{max} of Sacubitril is 1.75 hours and Valsartan is 3 hours. The Division of Bioequivalence/OGD will evaluate the bioequivalence study results and the biowaiver request.

4. **Dissolution Method:** (b)(4)
(b)(4) The originally proposed dissolution method was not acceptable (b)(4)

(b)(4)

In a response⁹ (dated February 24, 2020) to an Information Request, the Applicant adopted the new FDA dissolution database method (Table 2) (b)(4)

The Applicant also demonstrated the discriminating ability and suitability of the new dissolution method by comparing dissolution data of the exhibit batch of the 97 mg/103 mg strength vs. variant batches manufactured with changes in critical formulation variables (CFVs). It was found (b)(4)

⁶ Application 213719 - Sequence 0001 - 3.2.S.1.3 General Properties

⁷ Application 213719 - Sequence 0001 - 3.2.P.3.3 Description of Manufacturing Process and Process Controls

⁸ Application 213719 - Sequence 0001 - 3.2.P.1 Description and Composition of the Drug Product

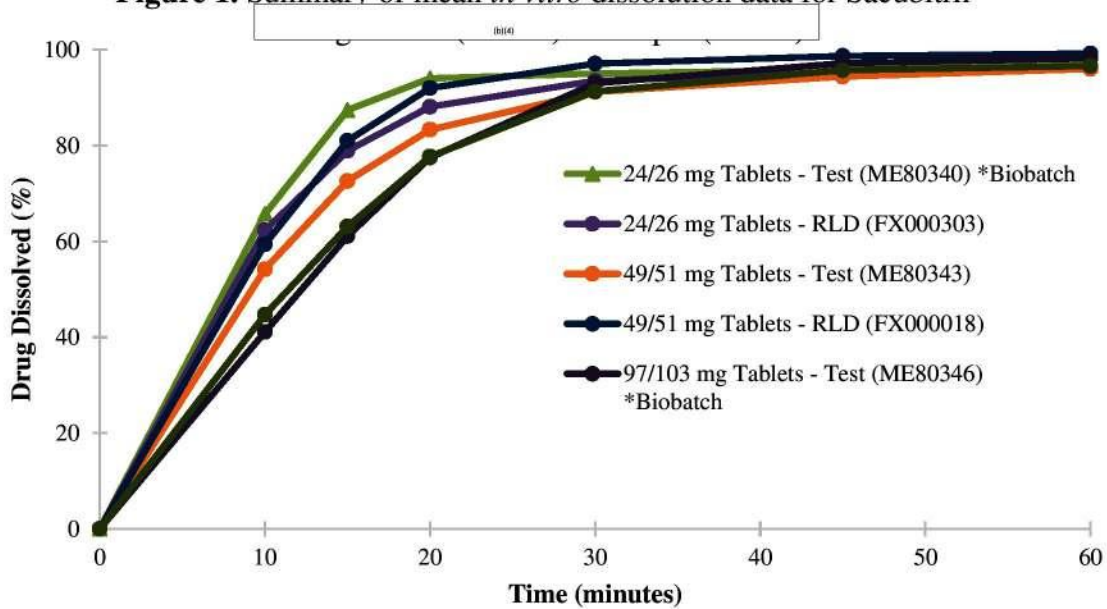
⁹ Application 213719 - Sequence 0007 - Cover Letter (0007) (02242020)

(b)(4)

5. **Dissolution Data:** The Applicant generated data using their originally proposed dissolution method [redacted]. It was noted

(b)(4)

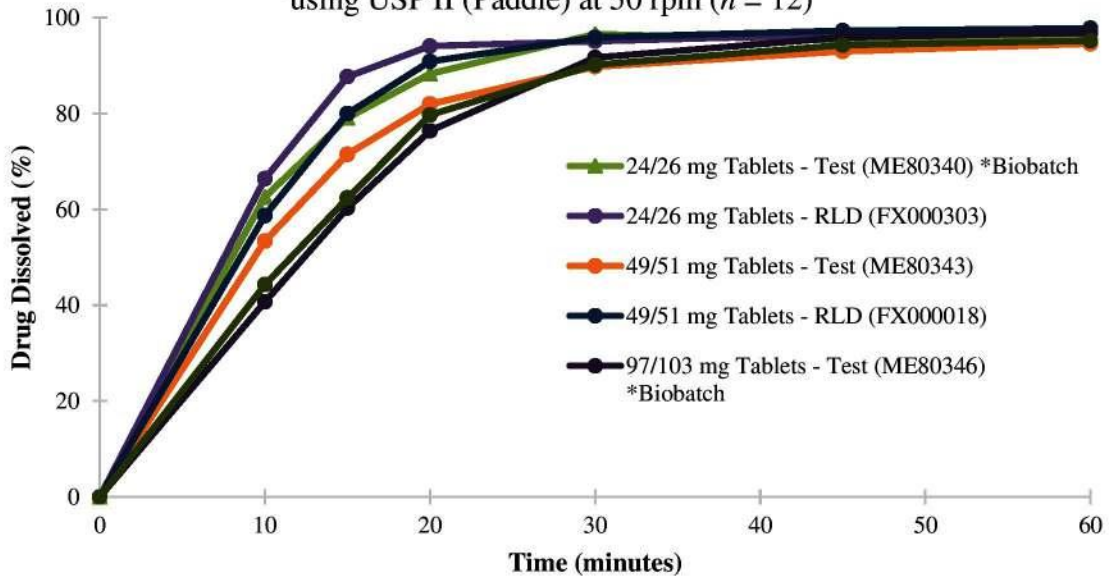
Figure 1. Summary of mean *in vitro* dissolution data for Sacubitril



¹⁰ [Application 213719 - Sequence 0007 - Dissolution Development Report](#)

¹¹ [Application 213719 - Sequence 0001 - 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods-pdf](#)

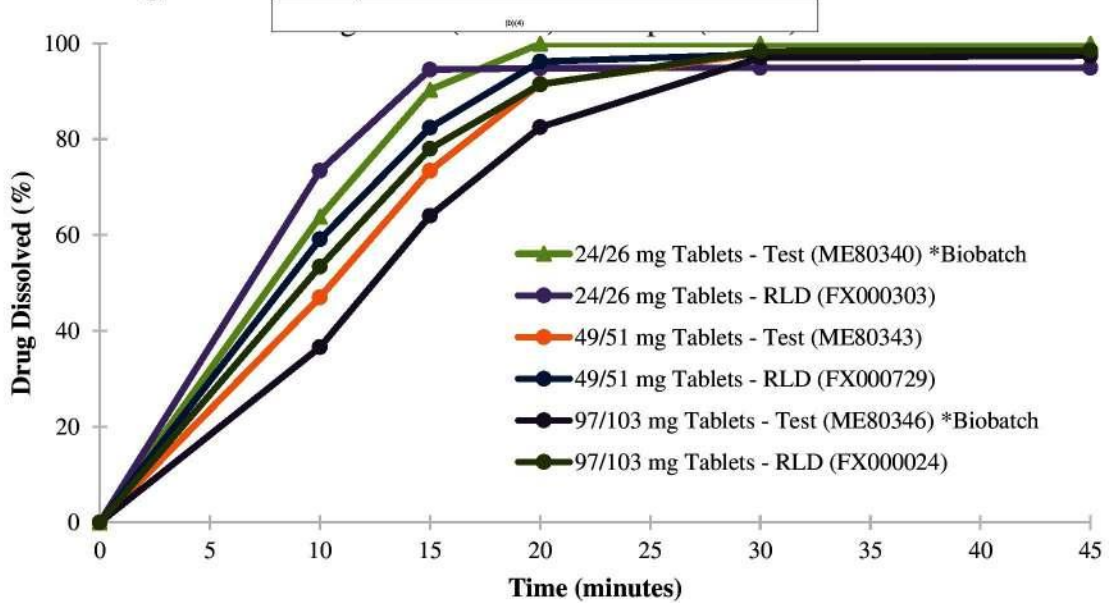
Figure 2. Summary of mean *in vitro* dissolution data for Valsartan using USP II (Paddle) at 50 rpm (*n* = 12)



In a response (dated February 24, 2020) to an Information Request, the Applicant

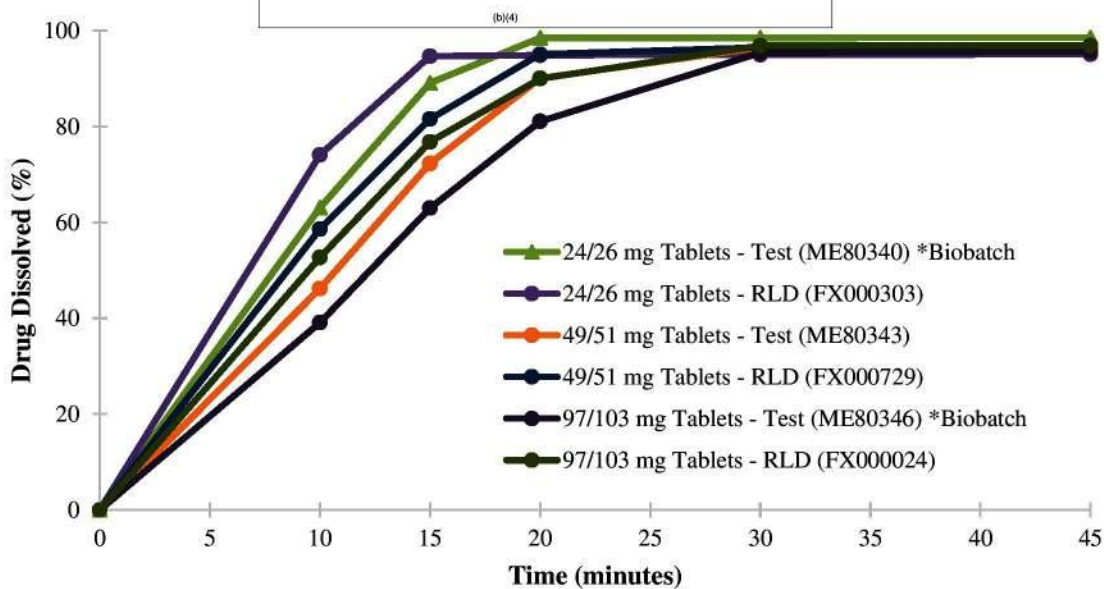
(b)(4)

Figure 3. Summary of mean *in vitro* dissolution data for Sacubitril



¹² Application 213719 - Sequence 0007 - Individual Unit Dissolution Data

Figure 4. Summary of mean *in vitro* dissolution data for Valsartan



6. **Dissolution Acceptance Criterion:** Based on the totality of the provided information and data, including BE studies on lowest and highest strength and the dissolution data, the proposed acceptance criterion of “NLT [redacted] % (Q) of Sacubitril and Valsartan in 30 minutes” using the newly proposed dissolution method is adequate for quality control testing of the proposed drug product.
7. **Dissolution in Stability:** The Applicant carried out dissolution stability studies on the exhibit batches in accelerated ($40^{\circ} \pm 2^{\circ}\text{C}/75\% \pm 5\% \text{RH}$) and long-term ($25^{\circ} \pm 2^{\circ}\text{C}/60\% \pm 5\% \text{RH}$) conditions.¹³ No significant changes in dissolution at [redacted] in stability in both accelerated and long-term conditions up to 6 months were observed using the originally proposed dissolution method. The 12 months old samples stored at long-term conditions also showed [redacted] dissolution using the newly proposed dissolution method.
8. **Dissolution Risk/Mitigation Assessment:** The Applicant provided information suggest that Sacubitril/Valsartan is considered [redacted]. However, the information available to the Reviewer indicate that the solubility is [redacted], and the proposed drug product has a relatively short T_{max} , therefore the risk is considered medium to high. The dissolution method and acceptance criteria are set appropriately to mitigate the risk of the change in the drug product performance.

Additional Note: [redacted]

(b)(4)

¹³ Application 213719 - Sequence 0001 - 3.2.P.8.1 Stability Summary and Conclusion

(b)(4)

The proposed test product is also showing incomplete dissolution with some of the strengths, which may be due to cone formation, because the formulation is similar to the NDA. Therefore, the Applicant was asked to conduct dissolution testing using the newly posted dissolution method.

Appendix 1: Biopharmaceutics Information Request

The following Biopharmaceutics Information Request (IR) comments were conveyed to the Applicant on December 23, 2019:

1. The proposed dissolution method (b)(4) (b)(4) is not acceptable at this stage because (b)(4)
(b)(4)

The limited data/information provided are not adequate to demonstrate the suitability/discriminating ability of the proposed dissolution method for your proposed drug product. Please note that the discriminating ability of the dissolution method should be investigated towards the critical material attributes (CMAs), critical process parameters (CPPs) and critical formulation variables (CFVs) which affect dissolution. In general, the testing conducted to demonstrate the discriminating ability of the dissolution method should compare the dissolution profiles of the proposed drug product(target) and the formulations/product that are intentionally manufactured with meaningful variations, i.e., aberrant formulations and manufacturing conditions with $\pm 10-20\%$ change to the specification-ranges of these variables for the most relevant CMA's and CPPs. Submit a separate dissolution method development report.

2. The dissolution data demonstrate that the dissolution of some units of the test product remains incomplete using your proposed method, for example some units of Batch #ME80343 (b)(4) The dissolution profiles of the exhibit batches, including the batch #ME80345, showed -- variability (b)(4)
(b)(4) In addition, there are differences between the dissolution profiles between the strengths of the proposed drug product. Explain the root cause of the incomplete dissolution and observed high variability of the proposed drug product using your proposed method. Support your explanation with appropriate data.

3. Note that the FDA dissolution database [https://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_SearchResults.cfm] has been updated with a new dissolution method [900 mL of Phosphate Buffer, pH 6.8 using USP apparatus 1 (basket) at 75 rpm]. Please submit dissolution data [(N=12, individual, mean, CV%)] for all your exhibits batches using this new dissolution method. If the dissolution of your proposed drug product remains incomplete or you notice cone formation using the originally proposed dissolution method (b)(4) then you may consider this new FDA database dissolution method (Basket/75 rpm) for the quality control testing of your proposed drug product.
 If you choose to follow this new FDA database dissolution method (Basket/75 rpm), then please submit the information/data showing the suitability/discriminating ability of the proposed dissolution method for your proposed drug product, as per above recommendations regarding the demonstration of the suitability/discriminating ability of the method.

The Applicant responded to the above Biopharmaceutics Information Request on February 24, 2020, provided additional dissolution data and information, adopted the new FDA dissolution database method for quality control testing of their proposed drug product, and accordingly updated the drug product release and stability specifications.¹⁴ The response is adequate.

¹⁴ [Application 213719 - Sequence 0007 - 3.2.P.5.1 Specification\(s\)](#)



Churg
Chan

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Om
Anand

Digitally signed by Om Anand
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Ragine
Maheswaran

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ANDA Executive Summary

1. Application/Product Information

ANDA Number.	213719										
Review Cycle #	04										
Applicant Name	ZYDUS PHARMACEUTICALS USA INC										
Drug Product Name	Sacubitril/Valsartan Tablets										
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: 194 mg; Valsartan: 206 mg										
Rx/OTC Dispensed	Rx										
Proposed Indication	(b)(4)										
Drug Product Description	<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr style="background-color: #e6e6fa;"> <th colspan="2" style="text-align: center;">Sacubitril/Valsartan Tablets</th> </tr> <tr style="background-color: #e0ffff;"> <th style="text-align: center;">Strength</th> <th style="text-align: center;">Product Description</th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">24 mg/26 mg</td> <td>White to off white colored film coated oval shaped, tablets debossed with "1272" on one side and plain on other side. (b)(4)</td> </tr> <tr> <td style="text-align: center;">49 mg/51 mg</td> <td>Brown to dark brown colored film coated oval shaped, tablets debossed with "1273" on one side and plain on other side. (b)(4)</td> </tr> <tr> <td style="text-align: center;">97 mg/103 mg</td> <td>Light orange to orange colored film coated oval shaped, tablets debossed with "1274" on one side and plain on other side. (b)(4)</td> </tr> </tbody> </table> (b)(4)	Sacubitril/Valsartan Tablets		Strength	Product Description	24 mg/26 mg	White to off white colored film coated oval shaped, tablets debossed with "1272" on one side and plain on other side. (b)(4)	49 mg/51 mg	Brown to dark brown colored film coated oval shaped, tablets debossed with "1273" on one side and plain on other side. (b)(4)	97 mg/103 mg	Light orange to orange colored film coated oval shaped, tablets debossed with "1274" on one side and plain on other side. (b)(4)
Sacubitril/Valsartan Tablets											
Strength	Product Description										
24 mg/26 mg	White to off white colored film coated oval shaped, tablets debossed with "1272" on one side and plain on other side. (b)(4)										
49 mg/51 mg	Brown to dark brown colored film coated oval shaped, tablets debossed with "1273" on one side and plain on other side. (b)(4)										
97 mg/103 mg	Light orange to orange colored film coated oval shaped, tablets debossed with "1274" on one side and plain on other side. (b)(4)										

	(b)(4)		
Co-packaged product information	N/A		
Device information, if any:	N/A		
Storage Temperature/ Conditions	25°C _± 2 °C/60% _± 5%RH		
Review Team	Discipline	Primary	Secondary
	<i>Drug Substance</i>	Baoqing Ma	Ragine Maheswaran
	<i>Drug Product/ Labeling</i>	Baoqing Ma	Ragine Maheswaran
	<i>Manufacturing</i>	Yeung Chan	Sridhar Thumma
	<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>	Qinghua Ge	
	<i>ATL</i>	Ragine Maheswaran	
Consults	Discipline Consulted	Recommendation	Date
	N/A	N/A	N/A

2. Submission Document(s) Reviewed

Submission(s) Assessed	Documents Date	Disciplines Affected
New application eCTD 0001	07/08/2019	All

Response to IRL eCTD 0002	09/06/2019	Quality
Response to DRL eCTD 0007	02/24/2020	Quality
Response to CRL eCTD 0009	12/28/2020	Quality
Response to CRL eCTD 0010	09/21/2021	Quality
Response to CRL eCTD 0014	06/14/2022	Quality
Response to IRL eCTD 0016	11/14/2022	Quality

3. Related/Supporting Documents

a. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Assessor/Comments
(b)(4)	II	(b)(4)	Sacubitril/Valsartan	Adequate	11/23/22	
	II		(b)(4)	AQAC	11/18/2022	
	III (if applicable)					
	IV (if applicable)					
	Other					

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

Document	Application Number	Description
NDA	207620	RLD Product (Entresto/Novartis)

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.*)

N/A

Drug Substance Deficiencies

N/A

Drug Product Deficiencies

N/A

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

N/A

Manufacturing Deficiencies

N/A

Biopharmaceutics Deficiencies

N/A

Microbiology Deficiencies

N/A

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)*

N/A

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:

In the previous cycle all disciplines are adequate except Facility was on withhold. In this cycle Facility is adequate. DMFs remain adequate.

b. Recommendation by Subdiscipline:

Drug Substance: ADEQUATE

Drug Product: ADEQUATE

Quality Labeling: ADEQUATE

Manufacturing: ADEQUATE

Biopharmaceutics: ADEQUATE

Microbiology: N/A

Environmental: ADEQUATE

6. Life-Cycle Considerations

**Established Conditions per ICH Q12: No
Comments:**

**Comparability Protocols (PACMP): No
Comments:**

Additional Comments: N/A



Ragine
Maheswaran

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MANUFACTURING INTEGRATED ASSESSMENT

Application ID	ANDA 213719
Drug Product Name	Sacubitril/Valsartan Tablets
Strengths	24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg
Dosage Form	Tablet
Administration Route	Oral
Indication	(b)(4)
Applicant Name	Zydus Pharmaceuticals (USA) Inc.
RLD Number	N207620

I. Manufacturing Summary

Facility Assessment Recommendation: Adequate

Process Assessment Recommendation: Adequate

Assessment Summary:

Process: Sacubitril and Valsartan Film-Coated Tablets (Sacubitril and Valsartan Tablets), 24/26 mg, 49/51 mg and 97/103 mg, a generic version of the Entresto® 24/26 mg, 49/51 mg and 97/103 mg. (b)(4)

(b)(4)

(b)(4) All process deficiencies were addressed by the firm's DRL response dated 02/24/2020.

Facility:

Third cycle review: Following a recently completed for-cause cGMP inspection on (b)(4)

(b)(4) has been changed to compliant and facility alert removed.

(b)(4) site is now acceptable for the proposed manufacturing operations as stated in ANDA 213719.

Overall, ANDA 213719 is recommended for approval from manufacturing perspective per Assessment #3.

First cycle review: (b)(4)

(b)(4)

(b)(4)

Second cycle review: (b)(4)

(b)(4)

List Submissions being assessed (Table):

Document Description (SD #)	Date Received
Original Submission (SD-1)	07/08/2019
IR response (SD-2)	09/06/2019
DRL response (SD-7)	02/24/2020
CR response (SD-9)	12/28/2020
CR response (SD-10)	09/21/2021
CR response (SD-14)	06/14/2022

Highlight Key Issues from Last Cycle and Their Resolution: Second Cycle Review

(b)(4)

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

Facility: *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
(b)(4)			Approve - Based on Previous History

(b)(4)	
	Approve - Based on PAI
	(b)(4)
	Approve - Based on PAI
	Other : Approve based on 704(a)(4) response

*Not for FOIA

(b)(4)

II. (b)(4) **Manufacturing**

1. Batch Formula

****** Response to DRL (SD-7) ******

Table 4: Batch Formula Details for (b)(4) for Sacubitril/Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg

Sr. No.	Name of Ingredient	Quantity / Unit (mg)			Quantity/Batch (kg)		%w/w
		24 mg/ 26 mg	49 mg/ 51 mg	97 mg/ 103 mg	Exhibit Batch	Intended Batch	
(b)(4)							
1	Sacubitril/Valsartan	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)
2	Microcrystalline Cellulose NF (b)(4)						
3	Low Substituted Hydroxy Propyl Cellulose NF (b)(4)						
4	Colloidal Silicon Dioxide, NF (b)(4)						
5	Sodium Stearyl Fumarate NF						
Total (Core Tablets)		90.250	180.500	361.000			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

VI. Signature Block

Round#	Primary Name	Secondary & Other Names	Date of Completion	Assessment Outcome	Facility OMIR
1	Teng Xu, Ph.D.	Vikas Moolchandani, Ph.D.	12/6/2019	IR	TBD
2	Teng Xu, Ph.D.	Vikas Moolchandani, Ph.D.	5/27/2020	CR Major	Withheld

		Jonathan Swoboda, Ph.D.			
3	Yoon Oh	Jonathan Swoboda	1/12/2021	CR Major	Withheld
4	Yeung Chan	Sridhar Thumma	12/21/2022	Adequate	Approve



Yeung
Chan

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Sridhar
Thumma

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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 213719 Assessment 03

Drug Product Name	Sacubitril/Valsartan
Dosage Form	Tablets
Strength	24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Zydus Pharmaceuticals (USA) Inc.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
New application eCTD 0001	07/08/2019	All
Response to IRL eCTD 0002	09/06/2019	Quality
Response to DRL eCTD 0007	02/24/2020	Quality
Response to CRL eCTD 0009	12/28/2020	Quality
Response to CRL eCTD 0010	09/21/2021	Quality

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	DMF reviewer	
Drug Product	Baoqing Ma	Ragine Maheswaran
Manufacturing	Yeung Chan	Yong Hu
Microbiology	N/A	N/A
Biopharmaceutics	Churg Chan	Om Anand
Regulatory Business Process Manager	Qinghua Ge	
Application Technical Lead	Ragine Maheswaran	
Laboratory (OTR)	N/A	N/A
Environmental	N/A	N/A

QUALITY ASSESSMENT DATA SHEET

For more details about the items in this template, please see the [Quality Assessment Data Sheet chapter of the ANDA IQA Guide](#)

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Assessor/Comments
	II		Sacubitril/Valsartan	Adequate	4/08/2022	
	III (if applicable)					
	IV (if applicable)					
	Other					

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

Document	Application Number	Description
NDA	207620	RLD Product (Entresto/Novartis)

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology	Complete	Adequate	3/26/2020	Saryu Goel
CDRH				
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 application is not approvable from quality perspective due to Facility related Major deficiencies.

II. QUALITY ASSESSMENT OVERVIEW

III. A. DP OVERALL RECOMMENDATION: Adequate

Drug Substance: Adequate

1. Provide Justification, if **Major**: (Click link to view [Justification Statements](#))

2. Insert additional **Major** justification below (if necessary)

Insert brief summary of Drug Substance assessment and deficiencies.

Drug Product: Adequate

1. Provide Justification, if **Major**: (Click link to view [Justification Statements](#))

2. Insert additional **Major** justification below (if necessary)

Insert brief summary of Drug Product assessment and deficiencies.

Labeling: Adequate

Insert brief summary of Labeling assessment and deficiencies.

B. Manufacturing:

a. Process: Adequate

1. Provide Justification, if **Major**: (Click link to view [Justification Statements](#))

2. Insert additional **Major** justification below (if necessary)

Summary:

Insert brief summary of Manufacturing Process assessment and deficiencies.

b. Facilities: Inadequate-Major

1. Provide Justification, if **Major**: ([Click link to view *Justification Statements*](#))

The facilities deficiencies have been classified as MAJOR because one or more facilities were found inadequate at the time of action due to inspectional deficiencies as noted in Appendix A, Section A(6)(a) of the Guidance for Industry, ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). Note that after the deficiencies have been purportedly resolved, FDA must assess the resolution of the cited deficiencies during the next review cycle. This assessment, upon receipt of an amendment responding to this deficiency, in FDA's judgement, will require substantial expenditure of FDA resources.

2. Insert additional **Major** justification below (if necessary)

Summary:

(b)(4)

(b)(4) *Satisfactory resolution of the observations is required before this ANDA may be approved*

C. Biopharmaceuticals: Adequate

1. Provide Justification, if **Major**: ([Click link to view *Justification Statements*](#))

2. Insert additional **Major** justification below (if necessary)

Insert brief summary of Biopharmaceuticals assessment and deficiencies.

D. Microbiology: Adequate

1. Provide Justification, if **Major**: ([Click link to view *Justification Statements*](#))

2. Insert additional **Major** justification below (if necessary)

Insert brief summary of Microbiology assessment and deficiencies.

E. List of Deficiencies for Complete Response

Overall Quality Deficiencies - Optional (*Deficiencies that affect multiple sub-disciplines*)

N/A

Drug Substance Deficiencies

N/A

Drug Product Deficiencies

N/A

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

N/A

Manufacturing Deficiencies

(b)(4)

Biopharmaceutics Deficiencies

N/A

Microbiology Deficiencies

N/A

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*)

N/A

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

***Application Technical Lead Name and Date: Ragine Maheswaran,
05/04/2022***



Ragine
Maheswaran

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CHAPTER I: DRUG SUBSTANCE

[IQA ANDA Assessment Guide Reference](#)

Drug Substance Name	Sacubitril/Valsartan Tablets	
ANDA Number	213719	
Applicant Name	ZYDUS PHARMACEUTICALS USA INC	
Assessment Cycle Number	3	
DMF Number (If Applicable)	(b)(4)	
DMF Status	Adequate	
DMF Status Date		
DMF Holder	(b)(4)	

Assessment Recommendation: Adequate

Theme:

☐ N/A	☐ Other (Requires Division Director Approval)
☐ DMF	☐ Due to Consult
☐ New DS Batch	

Justification: view justification statements found at: [Justification Statements](#)

Paste appropriate justification statement(s) here or insert "N/A" if not applicable.
Other (Requires Division Director Approval)- Assessor writes justification here if "other" selected as theme.

Assessment Summary:

Note:

Drug substance has no USP monograph. **DMF (b)(4) is adequate on 04/08/2022.**
 Drug product has no USP monograph.
 Drug substance and drug product have no comparability protocol or commitment. ICH Q3D information is satisfactory; Compliance statement included in specifications.

List Submissions being assessed (Table):

Document(s) Assessed	Date Received
Multiple Categories/Subcategories	9/21/2021
Multiple Categories/Subcategories	2/18/2022
Multiple Categories/Subcategories	2/24/2022

Multiple Categories/Subcategories	4/08/2022

List Submissions assessed (Table):

Document(s) Assessed	Date Received
Multiple Categories/Subcategories	12/28/2020
Amendment Correspondence/Amendment Verification Statement; Quality/Response to Discipline Review Letter	02/24/2020
Bioequivalence/Response to Discipline Review Letter; Amendment Correspondence/Amendment Verification Statement	01/09/2020
Quality/Facility Information; Amendment Correspondence/Amendment Verification Statement; Quality/Response To Information Request	09/06/2019
New/ANDA; Form 3674; User Fee/Coversheet	07/07/2019

Highlight Key Issues from Last Cycle and Their Resolution:

DMF is inadequate.

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

None

Select Number of Approved Comparability Protocols: 0

S.1 GENERAL INFORMATION

Summary of the Information

Drug Substance : Sacubitril/Valsartan

USAN : Sacubitril and Valsartan

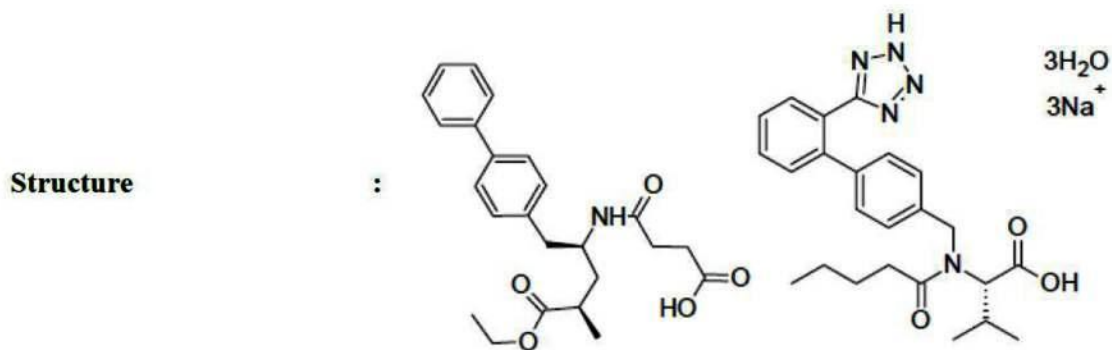
**Chemical Name/
IUPAC Name** : Trisodium [3-((1S,3R)-1-biphenyl-4-yl methyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3-methyl-2-(pentanoyl {2-(tetrazol-5-ylate)biphenyl-4-ylmethyl} amino)butyrate] trihydrate.

Synonyms : Sacubitril and Valsartan trisodium trihydrate

International Non-proprietary Name (INN) : Sacubitril/Valsartan

CAS Registry No. : 936623-90-4

Therapeutic category : Angiotensin receptor neprilysin inhibitor



Molecular Formula : $C_{48}H_{55}N_6Na_3O_8 \cdot 3H_2O$

Molecular Weight : 967

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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.

Assessment: Adequate

No comparability protocols were submitted.

Lifecycle Management Considerations

N/A.

DRUG SUBSTANCE LIST OF DEFICIENCIES

None

Primary Drug Substance Assessor Name and Date: Yang Yuan 11/24/2019; 3/23/2020; 4/16/2020.

Baoqing Ma, 7/26/2021 (12/28/2020 amendment), 4/13/2022.

Secondary Assessor Name and Date (and Secondary Summary, as needed): Matthew D. Vera, 12/13/2019; 4/22/2020, 6/11/2020.

Ragine Maheswaran, 7/26/2021 (12/28/2020 amendment), 4/13/2022.

CHAPTER II: DRUG PRODUCT

[IQA ANDA Assessment Guide Reference](#)

Product Information	Sacubitril/Valsartan Tablets
ANDA Number	213719
Assessment Cycle Number	2
Drug Product (DP) Name / Strength	Sacubitril/Valsartan Tablets 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg
Route of Administration	Oral
Drug Product Manufacturer	ZYDUS PHARMACEUTICALS USA INC
RLD/RS Information (Brand Name of Product, Applicant)	ENTRESTO® tablets
RLD/RS Number	N207620
Proposed Indication	(b)(4)

Assessment Recommendation: **Adequate**

Theme:

☐ N/A	☐ Unacceptable Analytical Methods
☐ Unqualified Impurity	☐ Application Quality
☐ New DP Batch	☐ Pharmaceutical Equivalence
☐ Product Design	☐ Product Safety
☐ Failing Stability Data	☐ Other (Requires Division Director Approval)
☐ Application Completeness	☐ Due to Consult

Justification: view justification statements found at: **[Justification Statements](#)**

Paste appropriate justification statement(s) here or insert "N/A" if not applicable.
Other (Requires Division Director Approval)- Assessor writes justification here if "other" selected as theme.

Assessment Summary:

Table 1. ANDA 213719/ Sacubitril/Valsartan Tablets

Drug Product CQAs	FMEC A RPN	Comment	Updated Risk Ranking after Review Cycle #1	Comments*
Physical stability (solid state)	12	(b)(4)	low	(b)(4)
Chemical Stability	24		low	
Assay	18		low	
Content uniformity	12		low	
Microbial limits	9		Low	
Dissolution	12		Low	

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Multiple Categories/Subcategories	12/28/2020
Amendment Correspondence/Amendment Verification Statement; Quality/Response to Discipline Review Letter	02/24/2020
Bioequivalence/Response to Discipline Review Letter; Amendment Correspondence/Amendment Verification Statement	01/09/2020
Quality/Facility Information; Amendment Correspondence/Amendment Verification Statement; Quality/Response To Information Request	09/06/2019
New/ANDA; Form 3674; User Fee/Coversheet	07/07/2019

Highlight Key Issues from Last Cycle and Their Resolution:

Concise Description of Outstanding Issues (*List Bullet Points with Key Information and Update as Needed*):

Select Number of Approved Comparability Protocols: 0

List Current Quality Endorsement Status:

- *USP monograph for Drug Product and compliance (current USP) – status: N/A.*
- *Dissolution status: specifications **are**/are not finalized with Biopharmaceutics, and implemented, and stability data complies with revised specifications (if applicable) to confirm shelf life proposal: Adequate.*
- *Elemental impurity compliance with ICH Q3D – status: Adequate.*
- *Number of Comparability protocols included: __0__*

P.1 DESCRIPTION AND COMPOSITION

Table 1: Description of the drug product

Sacubitril/Valsartan Tablets	
Strength	Product Description
24 mg/26 mg	White to off white colored film coated oval shaped, tablets debossed with “1272” on one side and plain on other side. (b)(4) (b)(4)
49 mg/51 mg	Brown to dark brown colored film coated oval shaped, tablets debossed with “1273” on one side and plain on other side. (b)(4) (b)(4)
97 mg/103 mg	Light orange to orange colored film coated oval shaped, tablets debossed with “1274” on one side and plain on other side. (b)(4) (b)(4)

Table 2: Photograph of test and RLD drug products for Sacubitril/Valsartan Tablets, 24 mg/26 mg

	Proposed Generic Product by Zydus [Sacubitril/Valsartan Tablets 24 mg/26 mg]	Reference Drug Product by Novartis Pharmaceuticals Corp [ENTRESTO[®] (sacubitril and valsartan) tablets, 24 mg/26 mg]
Identification Mark	White to off white colored film coated oval shaped, tablets debossed with “1272” on one side and plain on other side. (b)(4) (b)(4)	Violet white, unscored, ovaloid, biconvex, film-coated tablets, debossed with “NVR” on one side, and "LZ" on the other side
Visual Image	(b)(4)	

Table 3: Photograph of test and RLD drug products for Sacubitril/Valsartan Tablets, 49 mg/51 mg

	Proposed Generic Product by Zydus [Sacubitril/Valsartan Tablets, 49 mg/51 mg]	Reference Drug Product by Novartis Pharmaceuticals Corp [ENTRESTO® (sacubitril and valsartan) tablets, 49 mg/51 mg]
Identification Mark	Brown to dark brown colored film coated oval shaped, tablets debossed with “1273” on one side and plain on other side. (b)(4) (b)(4)	Pale yellow, unscored, ovaloid, biconvex, film-coated tablets, debossed with “NVR” on one side, and “L1” on the other side.
Visual Image	(b)(4)	

Table 4: Photograph of test and RLD drug products for Sacubitril/Valsartan Tablets, 97 mg/103 mg

	Proposed Generic Product by Zydus [Sacubitril/Valsartan Tablets, 97 mg/103 mg]	Reference Drug Product by Novartis Pharmaceuticals Corp [ENTRESTO® (sacubitril and valsartan) tablets, 97 mg/103 mg]
Identification Mark	Light orange to orange colored film coated oval shaped, tablets debossed with “1274” on one side and plain on other side. (b)(4) (b)(4)	Light pink, unscored, ovaloid, biconvex, film-coated tablets, debossed with “NVR” on one side, and “L11” on the other side.
Visual Image	(b)(4)	

Table 5: Size, Shape and Volume Comparison of the test and RLD drug products

Sr. No	Strength	Size and shape comparison				Volume comparison (mm ³)**		
		Dimension	Reference Product	Test Product	% difference in dimension	Reference Product	Test Product	% difference in Volume
1	24 mg/ 26 mg	Shape	Oval	Oval	NA	(b)(4)		
		Length (mm)	13.27	9.5	- 28.41%			
		Width (mm)	5.28	3.89	-26.33%			
		Thickness (mm)	3.64	3.33	- 8.52%			
2	49 mg/51 mg	Shape	Oval	Oval	NA			
		Length (mm)	13.24	13.18	+ 0.45%			
		Width (mm)	5.27	5.27	0.00%			
		Thickness (mm)	3.72	3.48	- 6.45%			
3	97 mg/103 mg	Shape	Oval	Oval	NA			
		Length (mm)	15.33	15.24	- 0.59%			
		Width (mm)	6.13	6.11	- 0.33%			
		Thickness (mm)	5.54	5.01	- 9.57%			

Component/Composition Table updated in 2/24/2020 submission (Seq. 0007)

Table 6: Qualitative and Quantitative composition per unit (mg/tablet)

Sr. No.	Name of Ingredient	Quantity per Unit (mg)			%w/w**			Function
		24 mg/26 mg	49 mg/51 mg	97 mg/103 mg	24 mg/26 mg	49 mg/51 mg	97 mg/103 mg	
Sacubitril/Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg								
1	Sacubitril/Valsartan* [®]	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	Active ingredient
2	Microcrystalline Cellulose NF							
3	Low Substituted Hydroxy Propyl Cellulose NF							
4	Colloidal Silicon Dioxide, NF							
5	Sodium Stearyl Fumarate NF							
(b)(4)								
Total (Core Tablet)		102.400	204.800	390.000	-	-	-	-

(b)(4)

Assessment: Adequate.

Sacubitril/Valsartan Tablets 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg, are oral shaped film-coated immediate release tablets. 24 mg/26 mg strength tablets are white to off-white color. 49 mg/51 mg strength tablets are brown to dark brown color. 97 mg/103 mg strength are light orange to orange color.

Sacubitril and valsartan tablets should contain 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 as per product labeling.

Firm provided the composition of the drug product table on page 9 of 16 in the [description and composition of the drug product.](#)

(b)(4)

Firm compared the tablets shape, color, size and thickness of the proposed drug product side by side with RLD drug products. The proposed 49 mg/51 mg and 97 mg/103 mg strength products are similar in size and shape to RLD. The proposed 24 mg/26 mg strength products are similar in shape to RLD, but the size is smaller. Therefore, the tablets size and shape met the requirements of FDA guidance. It is acceptable.

The excipients used are all commonly used compendial excipients. The excipients used in the proposed products are similar to those in RLD.

(b)(4)

(b)(4) Therefore, this product is similar in design to RLD.

Based on MDD of 194 mg of Sacubitril and 206 mg of Valsartan, firm stated none of the excipients exceeded the IIG limit for this route of administration. The assessment was covered in Bioequivalence review.

(b)(4)

Response is adequate.

Information Requested:

1. (b)(4)

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Methods Validation or Verification Package

Assessment: Refer to S.5 and P.5.

Comparability Protocols

Assessment: N/A.
No comparability protocols were provided.

Lifecycle Management Considerations

N/A.

DRUG PRODUCT LIST OF DEFICIENCIES

N/A

*Primary Drug Product Assessor Name and Date: Yang Yuan 12/4/2019; 4/2/2020
Baoqing Ma, 7/6/2021 (12/28/2020 amendment).*

*Secondary Assessor Name and Date (and Secondary Summary, as needed):
Matthew D. Vera, 12/16/2019; 4/22/2020, 6/11/2020.
Ragine Maheswaran, 7/16/2021 (12/28/2020 amendment).*

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	Length (MM)	Imprint Code
24 mg/26 mg	9.5 mm*3.89 mm*3.33 mm	"1272"
49 mg/51 mg	13.18 mm*5.27 mm*3.48 mm	"1273"
97 mg/103 mg	15.24 mm*6.11 mm*5.01 mm	"1274"

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:

An oral suspension dosing was added to the labeling as an alternative administration in 11/24/2019 submission. Firm provided adequate CMC study to support the oral suspension dosing. The assessment of CMC study is located in P2.

Issue Description	Issue Reference Number or Link
N/A	N/A

LABELING LIST OF DEFICIENCIES

Primary Drug Product Assessor Name and Date: Yang Yuan 12/5/2019; 4/24/2020

Secondary Drug Product Assessor Name and Date: Matthew D. Vera, 12/17/2019, 6/11/2020



Ragine
Maheswaran

Digitally signed by Ragine Maheswaran
Date: 4/14/2022 01:33:02PM
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Baoqing
Ma

Digitally signed by Baoqing Ma
Date: 4/14/2022 01:50:15PM
GUID: 57102a19005917e50cd92ae42839574a

MANUFACTURING INTEGRATED ASSESSMENT

Application ID	ANDA 213719
Drug Product Name	Sacubitril/Valsartan Tablets
Strengths	24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg
Dosage Form	Tablet
Administration Route	Oral
Indication	(b)(4)
Applicant Name	Zydus Pharmaceuticals (USA) Inc.
RLD Number	N207620

I. Manufacturing Summary

Facility Assessment Recommendation: Inadequate - Major

THEME: Inadequate Facility - cGMP Withhold and PAI 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:

Process: Sacubitril and Valsartan Film-Coated Tablets (Sacubitril and Valsartan Tablets), 24/26 mg, 49/51 mg and 97/103 mg, a generic version of the Entresto® 24/26 mg, 49/51 mg and 97/103 mg. (b)(4)

(b)(4)

Facility:

(b)(4)

(b)(4)

Second cycle review

(b)(4)

(b)(4)

List Submissions being assessed (Table):

Document Description (SD #)	Date Received
Original Submission (SD-1)	07/08/2019
IR response (SD-2)	09/06/2019
DRL response (SD-7)	02/24/2020
CR response (SD-9)	12/28/2020

Highlight Key Issues from Last Cycle and Their Resolution: N/A; First Cycle Review

(b)(4)

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

Facility:

DP manufacturing facility (Cadila Healthcare Limited/ FEI: 3002984011) was classified OAI based on the most recent surveillance inspection.

List Number of Comparability Protocols: None

1. Lifecycle Management Considerations

Post-approval inspection?	No
Lifecycle considerations	No

2. Facilities Table

Facility name and address	FEI	Responsibilities and profile code(s)	Status

(b)(4)	Withhold - Based on CGMP
	Approve - Based on PAI
	(b)(4)
	Approve - Based on PAI
	Other : Approve based on 704(a)(4) response
*-Not for FOIA:	
(b)(4)	

II. (b)(4) **Manufacturing**

1. Batch Formula

****** Response to DRL (SD-7) ******

Table 4: Batch Formula Details for for Sacubitril/Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg

Sr. No.	Name of Ingredient	Quantity / Unit (mg)			Quantity/Batch (kg)		%w/w
		24 mg/ 26 mg	49 mg/ 51 mg	97 mg/ 103 mg	Exhibit Batch	Intended Batch	
1	Sacubitril/Valsartan	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	
2	Microcrystalline Cellulose NF						
3	Low Substituted Hydroxy Propyl Cellulose NF						
4	Colloidal Silicon Dioxide, NF						
5	Sodium Stearyl Fumarate NF						
Total (Core Tablets)		90.250	180.500	361.000		100.00	

(b)(4)

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

(b) (4)

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(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	Teng Xu, Ph.D.	Vikas Moolchandani, Ph.D.	12/6/2019	IR	TBD
2	Teng Xu, Ph.D.	Vikas Moolchandani, Ph.D. Jonathan Swoboda, Ph.D.	5/27/2020	CR Major	Withheld
3	Yoon Oh	Jonathan Swoboda	1/12/2021	CR Major	Withheld



Yoon
Oh

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Date: 1/25/2021 12:31:21PM

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Jonathan
Swoboda

Digitally signed by Jonathan Swoboda

Date: 1/25/2021 01:17:55PM

GUID: 515203e500085f43a8035a5e00933ada

RECOMMENDATION

☐ Approval
☐ Complete Response-Minor
☒ Complete Response-Major
☐ Complete Response-Major-Facilities Only

ANDA 213719 Assessment #1

Drug Product Name	Sacubitril/Valsartan
Dosage Form	Tablets
Strength	24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Zydus Pharmaceuticals (USA) Inc. 73-B Route 31 North, Pennington, NJ 08534
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original ANDA	7/8/19	All
Response to Quality IR	9/6/19	Manufacturing
Response to Quality DRL	2/24/20	All

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Yanhong Li	Erin Skoda
Drug Product	Yang Yuan	Matthew Vera
Manufacturing	Teng (Daisy) Xu	Vikas Moolchandani Jonathan Swoboda
Microbiology	N/A	
Biopharmaceutics	Churg Chan	Om Anand
Regulatory Business Process Manager	Adrienne Belton	
Application Technical Lead	Matthew Vera	
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 Assessment Completed	Comments
(b)(4)	II	(b)(4)	Sacubitril/ Valsartan	Inadequate - Minor	4/15/2020	DMF CR letter issued 4/21/2020

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

Document	Application Number	Description
NDA	207620	RLD Product (Entresto/Novartis)

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology	Complete	Adequate	3/26/2020	Saryu Goel
CDRH-ODE				
CDRH-OC				
Clinical				
Other				

ABBREVIATED EXECUTIVE SUMMARY (CR ONLY)

[IQA ANDA Assessment Guide Reference](#)

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Major

This is a first-cycle Integrated Quality Assessment (IQA) of ANDA 213719, proposing Sacubitril/Valsartan tablets, 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg. The IQA team engaged the Applicant by Information Request Letter (9/3/2019) and Discipline Review Letter (12/23/2019) for resolution of potential deficiencies. The Applicant's responses resolved some but not all deficiencies.

OPQ recommends a Complete Response – Major letter due to the quality deficiencies outlined in Section II below.

II. QUALITY ASSESSMENT OVERVIEW

A. Drug Substance: Inadequate-Minor

(b)(4)

The Drug Substance section is Inadequate – Minor

Drug Product: Inadequate-Minor

(b)(4)

(b)(4)

The Drug Product section is Inadequate – Minor.

Labeling: Adequate

The labeling of the RLD Product Entresto (NDA 207620) was revised to include a dosage option requiring preparation of an oral suspension. The Applicant provided satisfactory study data to support the oral suspension dosing option.

No other quality-related labeling deficiencies were identified.

B. Manufacturing: Inadequate-Major

1. Primary Justification:

(b)(4)

Process:

(b)(4)

Facility:

(b)(4)

C. Biopharmaceutics: Adequate

(b)(4)

(b)(4)

(b)(4) to propose testing Sacubitril/Valsartan tablets using USP Apparatus I (Basket) (b)(4) The Applicant did not provide data supporting the suitability of the dissolution method. Therefore, in an Information Request dated December 23, 2019, the Applicant was recommended to investigate the discriminating ability of the method and explain the incomplete dissolution data of some units (b)(4) in the dissolution data of some batches. In a Response dated February 24, 2020, the Applicant adopted the new FDA dissolution database method (Table 2) (b)(4)

(b)(4)

(b)(4) The Applicant demonstrated discriminatory ability and suitability of the newly proposed dissolution method. Based on the provided information and data, the newly proposed dissolution method and acceptance criterion are acceptable for quality control testing of the proposed drug product.

From a Biopharmaceutics perspective, ANDA 213719 for the proposed Sacubitril/Valsartan Tablets, is adequate and recommended for approval.

The approved dissolution method and acceptance criterion for the proposed drug product are presented below:

Method Source	USP Apparatus	Speed	Medium	Volume/ Temperature	Acceptance Criterion [for both Sacubitril and Valsartan]
FDA – Database	I (Basket)	75 RPM	pH 6.8 phosphate buffer	900 mL/ 37°C ± 0.5°C	Q = □% in 30 minutes

D. Microbiology: N/A

A stand-alone microbiology review was not conducted (b)(4)
(b)(4) Please refer to the Process assessment for discussion of
microbial controls.

E. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies - Optional (Deficiencies that affect multiple sub-disciplines)

2. Drug Substance Deficiencies

1.

2.

(b)(4)

3. Drug Product Deficiencies

1.

2.

3.

4.

(b)(4)

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

None

5. Manufacturing Deficiencies

1.

2.

(b)(4)

3.

6. Biopharmaceutics Deficiencies

None

7. Microbiology Deficiencies

N/A

8. Other Deficiencies (Specify discipline, such as Environmental)

None

Application Technical Lead Name and Date: Matthew D. Vera, 7/1/2020



Matthew
Vera

Digitally signed by Matthew Vera

Date: 7/01/2020 12:02:01PM

GUID: 508da70c00028f2d4995c652b74162bc

CHAPTER I: DRUG SUBSTANCE

[IQA ANDA Assessment Guide Reference](#)

Drug Substance Name	Sacubitril/Valsartan Tablets	
ANDA Number	213719	
Applicant Name	ZYDUS PHARMACEUTICALS USA INC	
Assessment Cycle Number	1	
DMF Number (If Applicable)	(b)(4)	
DMF Status	Inadequate - Minor	
DMF Status Date	4/3/2018	
DMF Holder	(b)(4)	

Assessment Recommendation: Inadequate - Minor

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.

Assessment Summary:

Note:

Drug substance has no USP monograph. DMF# (b)(4) is inadequate on 04/15/2020.
 Drug product has no USP monograph.
 Drug substance and drug product have no comparability protocol or commitment. ICH Q3D information is satisfactory; Compliance statement included in specifications.

List Submissions being assessed (Table):

Document(s) Assessed	Date Received
Amendment Correspondence/Amendment Verification Statement;	02/24/2020

Quality/Response to Discipline Review Letter	
Bioequivalence/Response to Discipline Review Letter; Amendment Correspondence/Amendment Verification Statement	01/09/2020
Quality/Facility Information; Amendment Correspondence/Amendment Verification Statement; Quality/Response To Information Request	09/06/2019
New/ANDA; Form 3674; User Fee/Coversheet	07/07/2019

Highlight Key Issues from Last Cycle and Their Resolution:

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

Select Number of Approved Comparability Protocols: 0

S.1 GENERAL INFORMATION

Summary of the Information

Drug Substance : Sacubitril/Valsartan

USAN : Sacubitril and Valsartan

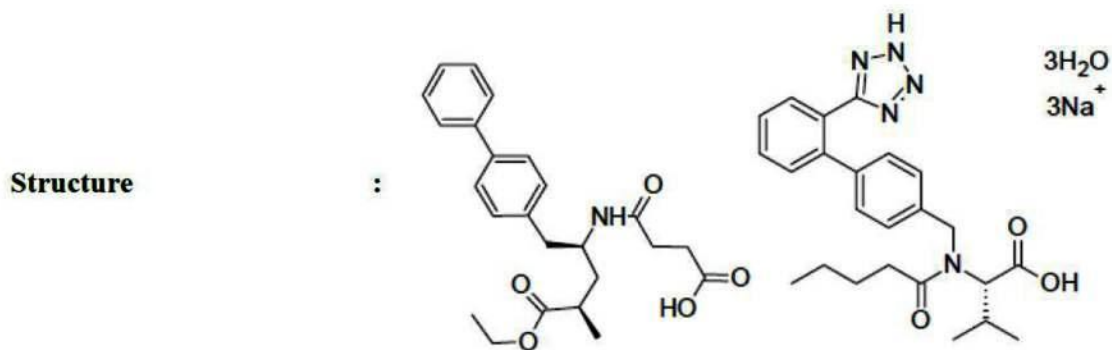
**Chemical Name/
IUPAC Name** : Trisodium [3-((1S,3R)-1-biphenyl-4-yl methyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3-methyl-2-(pentanoyl {2-(tetrazol-5-ylate)biphenyl-4-ylmethyl} amino)butyrate] trihydrate.

Synonyms : Sacubitril and Valsartan trisodium trihydrate

International Non-proprietary Name (INN) : Sacubitril/Valsartan

CAS Registry No. : 936623-90-4

Therapeutic category : Angiotensin receptor neprilysin inhibitor



Molecular Formula : $C_{48}H_{55}N_6Na_3O_8 \cdot 3H_2O$

Molecular Weight : 967

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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.

Lifecycle Management Considerations

N/A.

DRUG SUBSTANCE LIST OF DEFICIENCIES

1.	
2.	(b)(4)

*Primary Drug Substance Assessor Name and Date: Yang Yuan 11/24/2019;
3/23/2020; 4/16/2020*

*Secondary Assessor Name and Date (and Secondary Summary, as needed):
Matthew D. Vera, 12/13/2019; 4/22/2020, 6/11/2020*

CHAPTER II: DRUG PRODUCT

[IQA ANDA Assessment Guide Reference](#)

Product Information	Sacubitril/Valsartan Tablets
ANDA Number	213719
Assessment Cycle Number	1
Drug Product (DP) Name / Strength	Sacubitril/Valsartan Tablets 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg
Route of Administration	Oral
Drug Product Manufacturer	ZYDUS PHARMACEUTICALS USA INC
RLD/RS Information (Brand Name of Product, Applicant)	ENTRESTO® tablets
RLD/RS Number	N207620
Proposed Indication	(b)(4)

Assessment Recommendation: Inadequate - Minor

Theme:

☐ N/A	☐ Unacceptable Analytical Methods
☐ Unqualified Impurity	☐ Application Quality
☐ New DP Batch	☐ Pharmaceutical Equivalence
☐ Product Design	☐ Product Safety
☐ Failing Stability Data	☐ Other (Requires Division Director Approval)
☐ Application Completeness	☐ Due to Consult

Justification: view justification statements found at: [Justification Statements](#)

Paste appropriate justification statement(s) here or insert "N/A" if not applicable.
Other (Requires Division Director Approval)- Assessor writes justification here if "other" selected as theme.

Assessment Summary:

Table 1. ANDA 213719/ Sacubitril/Valsartan Tablets

Drug Product CQAs	FMEC A RPN	Comment	Updated Risk Ranking after Review Cycle #1	Comments*
Physical stability (solid state)	12	(b)(4)	low	(b)(4)
Chemical Stability	24		low	
Assay	18		low	
Content uniformity	12		low	
Microbial limits	9		Low	
Dissolution	12		Low	

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Amendment Correspondence/Amendment Verification Statement; Quality/Response to Discipline Review Letter	02/24/2020
Bioequivalence/Response to Discipline Review Letter; Amendment Correspondence/Amendment Verification Statement	01/09/2020
Quality/Facility Information; Amendment Correspondence/Amendment Verification Statement; Quality/Response To Information Request	09/06/2019
New/ANDA; Form 3674; User Fee/Coversheet	07/07/2019

Highlight Key Issues from Last Cycle and Their Resolution:

Concise Description of Outstanding Issues (*List Bullet Points with Key Information and Update as Needed*):

Select Number of Approved Comparability Protocols: 0

List Current Quality Endorsement Status:

- *USP monograph for Drug Product and compliance (current USP) – status: N/A.*
- *Dissolution status: specifications are/are not finalized with Biopharmaceutics, and implemented, and stability data complies with revised specifications (if applicable) to confirm shelf life proposal: Adequate.*
- *Elemental impurity compliance with ICH Q3D – status: Adequate.*
- *Number of Comparability protocols included: __0__*

P.1 DESCRIPTION AND COMPOSITION

Table 1: Description of the drug product

Sacubitril/Valsartan Tablets	
Strength	Product Description
24 mg/26 mg	White to off white colored film coated oval shaped, tablets debossed with “1272” on one side and plain on other side. (b)(4) (b)(4)
49 mg/51 mg	Brown to dark brown colored film coated oval shaped, tablets debossed with “1273” on one side and plain on other side. (b)(4) (b)(4)
97 mg/103 mg	Light orange to orange colored film coated oval shaped, tablets debossed with “1274” on one side and plain on other side. (b)(4) (b)(4)

Table 2: Photograph of test and RLD drug products for Sacubitril/Valsartan Tablets, 24 mg/26 mg

	Proposed Generic Product by Zydus [Sacubitril/Valsartan Tablets 24 mg/26 mg]	Reference Drug Product by Novartis Pharmaceuticals Corp [ENTRESTO[®] (sacubitril and valsartan) tablets, 24 mg/26 mg]
Identification Mark	White to off white colored film coated oval shaped, tablets debossed with “1272” on one side and plain on other side. (b)(4) (b)(4)	Violet white, unscored, ovaloid, biconvex, film-coated tablets, debossed with “NVR” on one side, and "LZ" on the other side
Visual Image	(b)(4)	

Table 3: Photograph of test and RLD drug products for Sacubitril/Valsartan Tablets, 49 mg/51 mg

	Proposed Generic Product by Zydus [Sacubitril/Valsartan Tablets, 49 mg/51 mg]	Reference Drug Product by Novartis Pharmaceuticals Corp [ENTRESTO® (sacubitril and valsartan) tablets, 49 mg/51 mg]
Identification Mark	Brown to dark brown colored film coated oval shaped, tablets debossed with “1273” on one side and plain on other side. (b)(4) (b)(4)	Pale yellow, unscored, ovaloid, biconvex, film-coated tablets, debossed with “NVR” on one side, and “L1” on the other side.
Visual Image	(b)(4)	

Table 4: Photograph of test and RLD drug products for Sacubitril/Valsartan Tablets, 97 mg/103 mg

	Proposed Generic Product by Zydus [Sacubitril/Valsartan Tablets, 97 mg/103 mg]	Reference Drug Product by Novartis Pharmaceuticals Corp [ENTRESTO® (sacubitril and valsartan) tablets, 97 mg/103 mg]
Identification Mark	Light orange to orange colored film coated oval shaped, tablets debossed with “1274” on one side and plain on other side (b)(4) (b)(4)	Light pink, unscored, ovaloid, biconvex, film-coated tablets, debossed with “NVR” on one side, and “L11” on the other side.
Visual Image	(b)(4)	

Table 5: Size, Shape and Volume Comparison of the test and RLD drug products

Sr. No	Strength	Size and shape comparison				Volume comparison (mm ³)**		
		Dimension	Reference Product	Test Product	% difference in dimension	Reference Product	Test Product	% difference in Volume
1	24 mg/ 26 mg	Shape	Oval	Oval	NA	(b)(4)		
		Length (mm)	13.27	9.5	- 28.41%			
		Width (mm)	5.28	3.89	-26.33%			
		Thickness (mm)	3.64	3.33	- 8.52%			
2	49 mg/51 mg	Shape	Oval	Oval	NA			
		Length (mm)	13.24	13.18	+ 0.45%			
		Width (mm)	5.27	5.27	0.00%			
		Thickness (mm)	3.72	3.48	- 6.45%			
3	97 mg/103 mg	Shape	Oval	Oval	NA			
		Length (mm)	15.33	15.24	- 0.59%			
		Width (mm)	6.13	6.11	- 0.33%			
		Thickness (mm)	5.54	5.01	- 9.57%			

Component/Composition Table updated in 2/24/2020 submission (Seq. 0007)

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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.

Comparability Protocols

Assessment: N/A.

No comparability protocols were provided.

Lifecycle Management Considerations

N/A.

DRUG PRODUCT LIST OF DEFICIENCIES

1.	(b)(4)
2.	
3.	
4.	

Primary Drug Product Assessor Name and Date: Yang Yuan 12/4/2019; 4/2/2020

*Secondary Assessor Name and Date (and Secondary Summary, as needed):
Matthew D. Vera, 12/16/2019; 4/22/2020, 6/11/2020*

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	Length (MM)	Imprint Code
24 mg/26 mg	9.5 mm*3.89 mm*3.33 mm	"1272"
49 mg/51 mg	13.18 mm*5.27 mm*3.48 mm	"1273"
97 mg/103 mg	15.24 mm*6.11 mm*5.01 mm	"1274"

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:

An oral suspension dosing was added to the labeling as an alternative administration in 11/24/2019 submission. Firm provided adequate CMC study to support the oral suspension dosing. The assessment of CMC study is located in P2.

Issue Description	Issue Reference Number or Link
N/A	N/A

LABELING LIST OF DEFICIENCIES

Primary Drug Product Assessor Name and Date: Yang Yuan 12/5/2019; 4/24/2020

Secondary Drug Product Assessor Name and Date: Matthew D. Vera, 12/17/2019, 6/11/2020



Matthew
Vera

Digitally signed by Matthew Vera

Date: 7/01/2020 12:03:35PM

GUID: 508da70c00028f2d4995c652b74162bc



Yang
Yuan

Digitally signed by Yang Yuan

Date: 7/01/2020 12:45:34PM

GUID: 55d356af000e98619d35dd54ab70b133

CHAPTER I: DRUG SUBSTANCE

[IQA ANDA Assessment Guide Reference](#)

Drug Substance Name	Sacubitril/Valsartan Tablets	
ANDA Number	213719	
Applicant Name	ZYDUS PHARMACEUTICALS USA INC	
Assessment Cycle Number	1	
DMF Number (If Applicable)	(b)(4)	
DMF Status	Inadequate - Minor	
DMF Status Date	7/22/2021	
DMF Holder	(b)(4)	

Assessment Recommendation: Inadequate - Minor

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.

Assessment Summary:

Note:

Drug substance has no USP monograph. DMF# (b)(4) is inadequate on 04/15/2020.

Drug product has no USP monograph.

Drug substance and drug product have no comparability protocol or commitment. ICH Q3D information is satisfactory; Compliance statement included in specifications.

List Submissions being assessed (Table):

Document(s) Assessed	Date Received
Multiple Categories/Subcategories	12/28/2020
Amendment Correspondence/Amendment Verification Statement;	02/24/2020

Quality/Response to Discipline Review Letter	
Bioequivalence/Response to Discipline Review Letter; Amendment Correspondence/Amendment Verification Statement	01/09/2020
Quality/Facility Information; Amendment Correspondence/Amendment Verification Statement; Quality/Response To Information Request	09/06/2019
New/ANDA; Form 3674; User Fee/Coversheet	07/07/2019

Highlight Key Issues from Last Cycle and Their Resolution:

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

Select Number of Approved Comparability Protocols: 0

S.1 GENERAL INFORMATION

Summary of the Information

Drug Substance : Sacubitril/Valsartan

USAN : Sacubitril and Valsartan

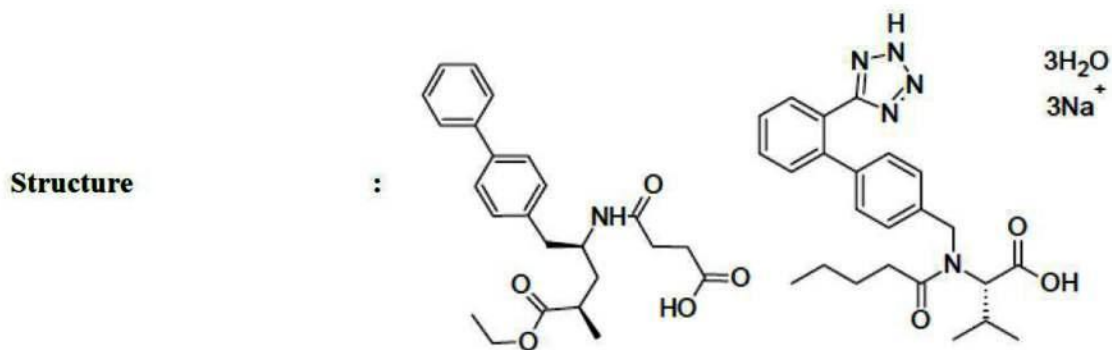
**Chemical Name/
IUPAC Name** : Trisodium [3-((1S,3R)-1-biphenyl-4-yl methyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3-methyl-2-(pentanoyl {2-(tetrazol-5-ylate)biphenyl-4-ylmethyl} amino)butyrate] trihydrate.

Synonyms : Sacubitril and Valsartan trisodium trihydrate

International Non-proprietary Name (INN) : Sacubitril/Valsartan

CAS Registry No. : 936623-90-4

Therapeutic category : Angiotensin receptor neprilysin inhibitor



Molecular Formula : $C_{48}H_{55}N_6Na_3O_8 \cdot 3H_2O$

Molecular Weight : 967

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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

No comparability protocols were submitted.

Lifecycle Management Considerations

N/A.

DRUG SUBSTANCE LIST OF DEFICIENCIES

I.

(b)(4)

Primary Drug Substance Assessor Name and Date: Yang Yuan 11/24/2019; 3/23/2020; 4/16/2020.

Baoqing Ma, 7/26/2021 (12/28/2020 amendment).

Secondary Assessor Name and Date (and Secondary Summary, as needed): Matthew D. Vera, 12/13/2019; 4/22/2020, 6/11/2020.

Ragine Maheswaran, 7/26/2021 (12/28/2020 amendment).

CHAPTER II: DRUG PRODUCT

[IQA ANDA Assessment Guide Reference](#)

Product Information	Sacubitril/Valsartan Tablets
ANDA Number	213719
Assessment Cycle Number	2
Drug Product (DP) Name / Strength	Sacubitril/Valsartan Tablets 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg
Route of Administration	Oral
Drug Product Manufacturer	ZYDUS PHARMACEUTICALS USA INC
RLD/RS Information (Brand Name of Product, Applicant)	ENTRESTO® tablets
RLD/RS Number	N207620
Proposed Indication	(b)(4)

Assessment Recommendation: Adequate

Theme:

☐ N/A	☐ Unacceptable Analytical Methods
☐ Unqualified Impurity	☐ Application Quality
☐ New DP Batch	☐ Pharmaceutical Equivalence
☐ Product Design	☐ Product Safety
☐ Failing Stability Data	☐ Other (Requires Division Director Approval)
☐ Application Completeness	☐ Due to Consult

Justification: view justification statements found at: [Justification Statements](#)

Paste appropriate justification statement(s) here or insert "N/A" if not applicable.
Other (Requires Division Director Approval)- Assessor writes justification here if "other" selected as theme.

Assessment Summary:

Table 1. ANDA 213719/ Sacubitril/Valsartan Tablets

Drug Product CQAs	FMEC A RPN	Comment	Updated Risk Ranking after Review Cycle #1	Comments*
Physical stability (solid state)	12	(b)(4)	low	(b)(4)
Chemical Stability	24		low	
Assay	18		low	
Content uniformity	12		low	
Microbial limits	9		Low	
Dissolution	12		Low	

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Multiple Categories/Subcategories	12/28/2020
Amendment Correspondence/Amendment Verification Statement; Quality/Response to Discipline Review Letter	02/24/2020
Bioequivalence/Response to Discipline Review Letter; Amendment Correspondence/Amendment Verification Statement	01/09/2020
Quality/Facility Information; Amendment Correspondence/Amendment Verification Statement; Quality/Response To Information Request	09/06/2019
New/ANDA; Form 3674; User Fee/Coversheet	07/07/2019

Highlight Key Issues from Last Cycle and Their Resolution:

Concise Description of Outstanding Issues (*List Bullet Points with Key Information and Update as Needed*):

Select Number of Approved Comparability Protocols: 0

List Current Quality Endorsement Status:

- *USP monograph for Drug Product and compliance (current USP) – status: N/A.*
- *Dissolution status: specifications **are**/are not finalized with Biopharmaceutics, and implemented, and stability data complies with revised specifications (if applicable) to confirm shelf life proposal: Adequate.*
- *Elemental impurity compliance with ICH Q3D – status: Adequate.*
- *Number of Comparability protocols included: __0__*

P.1 DESCRIPTION AND COMPOSITION

Table 1: Description of the drug product

Sacubitril/Valsartan Tablets	
Strength	Product Description
24 mg/26 mg	White to off white colored film coated oval shaped, tablets debossed with “1272” on one side and plain on other side. (b)(4) (b)(4)
49 mg/51 mg	Brown to dark brown colored film coated oval shaped, tablets debossed with “1273” on one side and plain on other side. (b)(4) (b)(4)
97 mg/103 mg	Light orange to orange colored film coated oval shaped, tablets debossed with “1274” on one side and plain on other side. (b)(4) (b)(4)

Table 2: Photograph of test and RLD drug products for Sacubitril/Valsartan Tablets, 24 mg/26 mg

	Proposed Generic Product by Zydus [Sacubitril/Valsartan Tablets 24 mg/26 mg]	Reference Drug Product by Novartis Pharmaceuticals Corp [ENTRESTO[®] (sacubitril and valsartan) tablets, 24 mg/26 mg]
Identification Mark	White to off white colored film coated oval shaped, tablets debossed with “1272” on one side and plain on other side. (b)(4)	Violet white, unscored, ovaloid, biconvex, film-coated tablets, debossed with “NVR” on one side, and "LZ" on the other side
Visual Image	(b)(4)	

Table 3: Photograph of test and RLD drug products for Sacubitril/Valsartan Tablets, 49 mg/51 mg

	Proposed Generic Product by Zydus [Sacubitril/Valsartan Tablets, 49 mg/51 mg]	Reference Drug Product by Novartis Pharmaceuticals Corp [ENTRESTO® (sacubitril and valsartan) tablets, 49 mg/51 mg]
Identification Mark	Brown to dark brown colored film coated oval shaped, tablets debossed with “1273” on one side and plain on other side. (b)(4) (b)(4)	Pale yellow, unscored, ovaloid, biconvex, film-coated tablets, debossed with “NVR” on one side, and “L1” on the other side.
Visual Image	(b)(4)	

Table 4: Photograph of test and RLD drug products for Sacubitril/Valsartan Tablets, 97 mg/103 mg

	Proposed Generic Product by Zydus [Sacubitril/Valsartan Tablets, 97 mg/103 mg]	Reference Drug Product by Novartis Pharmaceuticals Corp [ENTRESTO® (sacubitril and valsartan) tablets, 97 mg/103 mg]
Identification Mark	Light orange to orange colored film coated oval shaped, tablets debossed with “1274” on one side and plain on other side. (b)(4) (b)(4)	Light pink, unscored, ovaloid, biconvex, film-coated tablets, debossed with “NVR” on one side, and “L11” on the other side.
Visual Image	(b)(4)	

Table 5: Size, Shape and Volume Comparison of the test and RLD drug products

Sr. No	Strength	Size and shape comparison				Volume comparison (mm ³)**		
		Dimension	Reference Product	Test Product	% difference in dimension	Reference Product	Test Product	% difference in Volume
1	24 mg/26 mg	Shape	Oval	Oval	NA	(b)(4)		
		Length (mm)	13.27	9.5	-28.41%			
		Width (mm)	5.28	3.89	-26.33%			
		Thickness (mm)	3.64	3.33	-8.52%			
2	49 mg/51 mg	Shape	Oval	Oval	NA			
		Length (mm)	13.24	13.18	+0.45%			
		Width (mm)	5.27	5.27	0.00%			
		Thickness (mm)	3.72	3.48	-6.45%			
3	97 mg/103 mg	Shape	Oval	Oval	NA			
		Length (mm)	15.33	15.24	-0.59%			
		Width (mm)	6.13	6.11	-0.33%			
		Thickness (mm)	5.54	5.01	-9.57%			

Component/Composition Table updated in 2/24/2020 submission (Seq. 0007)

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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.

Methods Validation or Verification Package

Assessment: Refer to S.5 and P.5.

Comparability Protocols

Assessment: N/A.
No comparability protocols were provided.

Lifecycle Management Considerations

N/A.

DRUG PRODUCT LIST OF DEFICIENCIES

N/A

*Primary Drug Product Assessor Name and Date: Yang Yuan 12/4/2019; 4/2/2020
Baoqing Ma, 7/6/2021 (12/28/2020 amendment).*

*Secondary Assessor Name and Date (and Secondary Summary, as needed):
Matthew D. Vera, 12/16/2019; 4/22/2020, 6/11/2020.
Ragine Maheswaran, 7/16/2021 (12/28/2020 amendment).*

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	Length (MM)	Imprint Code
24 mg/26 mg	9.5 mm*3.89 mm*3.33 mm	"1272"
49 mg/51 mg	13.18 mm*5.27 mm*3.48 mm	"1273"
97 mg/103 mg	15.24 mm*6.11 mm*5.01 mm	"1274"

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:

An oral suspension dosing was added to the labeling as an alternative administration in 11/24/2019 submission. Firm provided adequate CMC study to support the oral suspension dosing. The assessment of CMC study is located in P2.

Issue Description	Issue Reference Number or Link
N/A	N/A

LABELING LIST OF DEFICIENCIES

Primary Drug Product Assessor Name and Date: Yang Yuan 12/5/2019; 4/24/2020

Secondary Drug Product Assessor Name and Date: Matthew D. Vera, 12/17/2019, 6/11/2020



Ragine
Maheswaran

Digitally signed by Ragine Maheswaran
Date: 7/27/2021 11:53:14AM
GUID: 508da703000288694c718e4706287c61



Baoqing
Ma

Digitally signed by Baoqing Ma
Date: 7/27/2021 01:54:14PM
GUID: 57102a19005917e50cd92ae42839574a

MANUFACTURING INTEGRATED ASSESSMENT

Application ID	ANDA 213719
Drug Product Name	Sacubitril/Valsartan Tablets
Strengths	24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg
Dosage Form	Tablet
Administration Route	Oral
Indication	(b)(4)
Applicant Name	Zydus Pharmaceuticals (USA) Inc.
RLD Number	N207620

I. Manufacturing Summary

Facility Assessment Recommendation: Inadequate - Major

THEME: Inadequate Facility - cGMP Withhold and PAI 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:

Process: Sacubitril and Valsartan Film-Coated Tablets (Sacubitril and Valsartan Tablets), 24/26 mg, 49/51 mg and 97/103 mg. a generic version of the Entresto® 24/26 mg, 49/51 mg and 97/103 mg. (b)(4)

(b)(4)

Facility:

Following a review of the inspectional histories of the drug substance and drug product manufacturing and testing facilities, (b)(4)

(b)(4)

(b)(4)

List Submissions being assessed (Table):

Document Description (SD #)	Date Received
Original Submission (SD-1)	07/08/2019
IR response (SD-2)	09/06/2019
DRL response (SD-7)	02/24/2020

Highlight Key Issues from Last Cycle and Their Resolution: N/A; First Cycle Review

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

Process: All process deficiencies were addressed by the firm's DRL response dated 02/24/2020.

Facility:

- (b)(4)
- (b)(4)

List Number of Comparability Protocols: None

1. Lifecycle Management Considerations

Post-approval inspection?	No
Lifecycle considerations	No

2. Facilities Table

Facility name and address	FEI	Responsibilities and profile code(s)	Status
(b)(4)			Withhold - Based on CGMP
			Approve - Based on PAI

(b)(4)	Approve - Based on Previous History
	Withhold - Based on PAI

* Not for FOIA (b)(4)

(b)(4)

II. (b)(4) Manufacturing

1. Batch Formula

****** Response to DRL (SD-7) ******

Table 4: Batch Formula Details for (b)(4) for Sacubitril/Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg

Sr. No.	Name of Ingredient	Quantity / Unit (mg)			Quantity/Batch (kg)		%w/w
		24 mg/ 26 mg	49 mg/ 51 mg	97 mg/ 103 mg	Exhibit Batch	Intended Batch	
1	Sacubitril/Valsartan	(b)(4)			(b)(4)		(b)(4)
2	Microcrystalline Cellulose NF						
3	Low Substituted Hydroxy Propyl Cellulose NF						
4	Colloidal Silicon Dioxide, NF						
5	Sodium Stearyl Fumarate NF						
Total (Core Tablets)		90.250	180.500	361.000			100.00

(b)(4)



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

(b) (4)

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

(b)(4)

VI. Signature Block

Round#	Primary Name	Secondary & Other Names	Date of Completion	Assessment Outcome	Facility OMIR
1	Teng Xu, Ph.D.	Vikas Moolchandani, Ph.D.	12/6/2019	IR	TBD
2	Teng Xu, Ph.D.	Vikas Moolchandani, Ph.D. Jonathan Swoboda, Ph.D.	5/27/2020	CR Major	Withheld



Teng (Daisy)
Xu

Digitally signed by Teng (Daisy) Xu
Date: 5/27/2020 11:53:14AM
GUID: 5aaa8fe80050c0044b390b1800e17fa6



Jonathan
Swoboda

Digitally signed by Jonathan Swoboda
Date: 5/27/2020 12:24:54PM
GUID: 515203e500085f43a8035a5e00933ada



Vikas
Moolchandani

Digitally signed by Vikas Moolchandani
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M E M O R A N D U M

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

DATE: August 29, 2019

TO: Bing Li, Ph.D.
Director (Acting)
Office of Bioequivalence
Office of Generic Drugs

FROM: Xingfang Li, MD, RAC
Pharmacologist
Division of Generic Drug Bioequivalence Evaluation
(DGDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: John A. Kadavil, Ph.D.
Deputy Director
DGDBE, OSIS

SUBJECT: Routine inspection of Cliantha Research Ltd,
Vadodara, Gujarat, India

1 Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged a clinical inspection of the following studies at Cliantha Research, Ltd., in Vadodara, Gujarat, India.

No objectionable conditions were observed and Form FDA 483 was not issued at the inspection close-out. The final inspection classification is No Action Indicated (NAI).

1.1 Recommendation

After reviewing the inspectional findings, I conclude that data from the audited studies are reliable to support a regulatory decision.

2 Inspected Studies:

(b)(4)

(b)(4)

3 Inspectional Findings

At the conclusions of this inspection, investigator Kilili did not observe objectionable conditions and did not issue Form FDA 483 to the clinical site.

4 Conclusion

After reviewing the inspectional findings, I conclude that the data from studies to support [REDACTED] are reliable. In addition, the data from studies of similar design that were not audited but submitted to pending applications (**Attachment 1**) are reliable for Agency review.

Based on the inspectional findings, studies of similar design conducted between the previous inspection [REDACTED] and the end of the current surveillance interval should be considered reliable without an inspection.

Xingfang Li, MD, RAC
Pharmacologist
DGDBE, OSIS

Final Classification:

NAI- Cliantha Research Ltd
Vadodara, Gujarat, India
FEI#: 3007078964

cc:

OTS/OSIS/Kassim/Dasgupta/Mitchell/Fenty-Stewart/Taylor/Haidar/
Mirza

OTS/OSIS/DNDBE/Bonapace/Au/Ayala/Biswas

OTS/OSIS/DGDBE/Cho/Kadavil/Choi/Skelly/Li

FDAInternationalBIMO@fda.hhs.gov

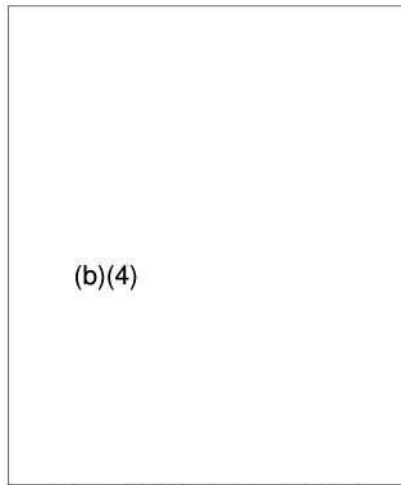
Draft: XFL 8/23/2019

Edit: MFS 8/23/2019; JAK 8/26/2019

ECMS: Cabinets/CDER_OTS/Office of Study Integrity and
Surveillance/INSPECTIONS/BE Program/CLINICAL/Cliantha Research,
Ltd., (1st Floor, Silver Arcade) Vadodara, Gujarat, India

file #:

[REDACTED]
(b)(4)



8658 (ANDA 213719)



FACTS: 11916058

Xingfang Li -S Digitally signed by Xingfang Li -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Xingfang Li -S,
0.9.2342.19200300.100.1.1=2000576511
Date: 2019.08.29 08:01:21 -04'00'

Name

Michael F. Skelly -S Digitally signed by Michael F. Skelly -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300099113,
cn=Michael F. Skelly -S
Date: 2019.08.29 09:00:43 -04'00'

Name

John A. Kadavil -S Digitally signed by John A. Kadavil -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300217653,
cn=John A. Kadavil -S
Date: 2019.08.29 09:21:18 -04'00'

Name

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(b) (4)

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(b)(4)

ANDA 213719	BA18086667 BA18086532 BA17861024-01	Sacubitril and Valsartan Tablets	(b)(4)

(b)(4)

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:

(b)(4)

ANDA 213719

(b)(4)

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 [REDACTED], which falls within the surveillance interval. The inspection was conducted under the following submissions: ANDAs [REDACTED]

The final classification for the inspection was No Action Indicated (NAI).

Therefore, based on the rationale described above, an inspection is not warranted at this time.

Inspection Site

Facility Type	Facility Name	Facility Address
Analytical	(b)(4)	

Timely Consults and Early IR Checklist for Type II API DMFs

Result: TCIR-Hidden Facility/Intermediate Facility Evaluated

ANDA#: 213719

Drug Product: SACUBITRIL AND VALSARTAN, tablet, 49mg || 51mg || 97mg || 103mg
|| 24mg || 26mg

DMF#:

DMF Subject (API name): SACUBITRIL/VALSARTAN

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 DMF also includes the manufacturing information for sacubitril from an advanced intermediate and for Valsartan from starting materials. This is a violation of the GDUFA provision for the DMF to contain manufacturing information for only one API (the complex in not considered the API). Valsartan and Sacubitril are isolated materials prior to complex formation so sameness should not be an issue for either API. No DMF is referenced for the advanced sacubitril intermediate, however they do identify the manufacturing facility for this material. The manufacturing facility for valsartan, sacubitril, and the complex is already included in the 356h form.

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: 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 is a manufacturing facility (critical intermediate) that is included in DMF [redacted] for SACUBITRIL/VALSARTAN that is 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

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:

3. 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: 7/19/2019 05:31:33PM
GUID: 508da7020002879dab02d51b50cc9c3d

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 213719

BIOEQUIVALENCE REVIEW(s)

BIOPHARMACEUTICS ANDA REVIEW	
Application No.	ANDA-213719-ORIG-1
Applicant	Zydus Pharmaceuticals (USA) Inc.
Product Name/ Strength(s)	Sacubitril/Valsartan Tablets 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg
Dosage Form/Route	Immediate-release tablet/Oral
Indication	Reduce the risk of cardiovascular death and hospitalization for heart failure
Submission Date(s)	7/8/2019 – Original Submission 2/24/2020 – 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 criterion for quality control testing of the proposed drug product.

Dissolution Method and Acceptance Criterion:

(b)(4)

The FDA’s dissolution database was updated on October 24, 2019 to propose testing Sacubitril/Valsartan tablets using USP Apparatus I (Basket) (b)(4). The Applicant did not provide data supporting the suitability of the dissolution method. Therefore, in an Information Request dated December 23, 2019, the Applicant was recommended to investigate the discriminating ability of the method and explain the incomplete dissolution data of some units and (b)(4) in the dissolution data of some batches. In a Response dated February 24, 2020, the Applicant adopted the new FDA dissolution database method (Table 2) (b)(4).

(b)(4)

(b)(4) The Applicant demonstrated discriminatory ability and suitability of the newly proposed dissolution method. Based on the provided information and data, the newly proposed dissolution method and acceptance criterion are acceptable for quality control testing of the proposed drug product.

¹ [FDA Recommended Dissolution Methods](#)

² [Application 213719 - Sequence 0007 - Cover Letter \(0007\) \(02242020\)](#)

Table 1. Originally proposed dissolution method and acceptance criterion by the Applicant³

Method Source	USP Apparatus	Speed	Medium	Volume/ Temperature	Proposed Acceptance Criteria
(b)(4)					

Recommendation:

From a Biopharmaceutics perspective, ANDA 213719 for the proposed Sacubitril/Valsartan Tablets, is **adequate** and recommended for **approval**.

The approved dissolution method and acceptance criterion for the proposed drug product are presented below:

Table 2. Approved dissolution method and acceptance criterion⁵

Method Source	USP Apparatus	Speed	Medium	Volume/ Temperature	Acceptance Criterion [for both Sacubitril and Valsartan]
FDA – Database	I (Basket)	75 RPM	pH 6.8 phosphate buffer	900 mL/ 37°C ± 0.5°C	Q = □% in 30 minutes

³ [Application 213719 - Sequence 0001 - 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods-pdf](#)

⁴ Previous method

⁵ [Application 213719 - Sequence 0007 - Dissolution Development Report](#)

BIOPHARMACEUTICS REVIEW

1. **Drug Substance Solubility:** The Applicant submitted solubility data for Sacubitril and Valsartan,

(b)(4)

2. **Formulation:** The proposed product is

(b)(4)

3. **Bioequivalence and PK Characteristics:** The Applicant performed *in vivo* pharmacokinetic studies using the 97 mg/103 mg tablets of the proposed and RLD products in both fasting and fed conditions. The Applicant performed another *in vivo* pharmacokinetic study using the lower strength of 24/26 mg tablet of the proposed and RLD product under fasting conditions. Under fasting conditions, the T_{max} of Sacubitril is 0.5 hours and Valsartan is 1.75 hours. Under fed conditions, the T_{max} of Sacubitril is 1.75 hours and Valsartan is 3 hours. The Division of Bioequivalence/OGD will evaluate the bioequivalence study results and the biowaiver request.

4. **Dissolution Method:**

(b)(4)

In a response⁹ (dated February 24, 2020) to an Information Request, the Applicant adopted the new FDA dissolution database method (Table 2)

The Applicant also demonstrated the discriminating ability and suitability of the new dissolution method by comparing dissolution data of the exhibit batch of the 97 mg/103 mg strength vs. variant batches manufactured with changes in critical formulation variables (CFVs). It was found that dissolution was seen with

⁶ [Application 213719 - Sequence 0001 - 3.2.S.1.3 General Properties](#)

⁷ [Application 213719 - Sequence 0001 - 3.2.P.3.3 Description of Manufacturing Process and Process Controls](#)

⁸ [Application 213719 - Sequence 0001 - 3.2.P.1 Description and Composition of the Drug Product](#)

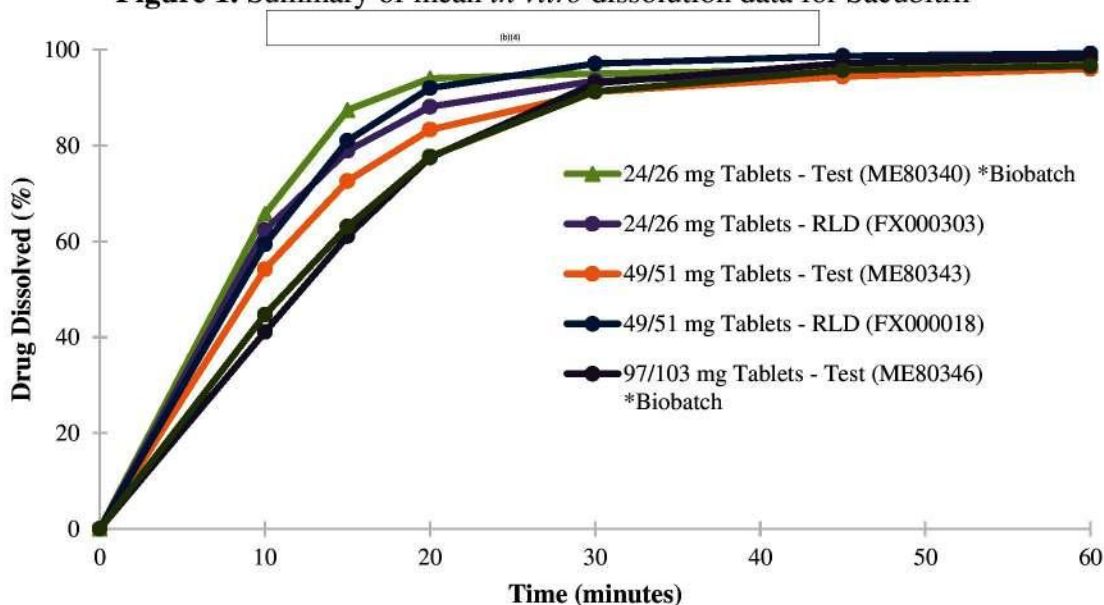
⁹ [Application 213719 - Sequence 0007 - Cover Letter \(0007\) \(02242020\)](#)

(b)(4)

5. **Dissolution Data:** The Applicant generated data using their originally proposed dissolution method [redacted] It was noted

(b)(4)

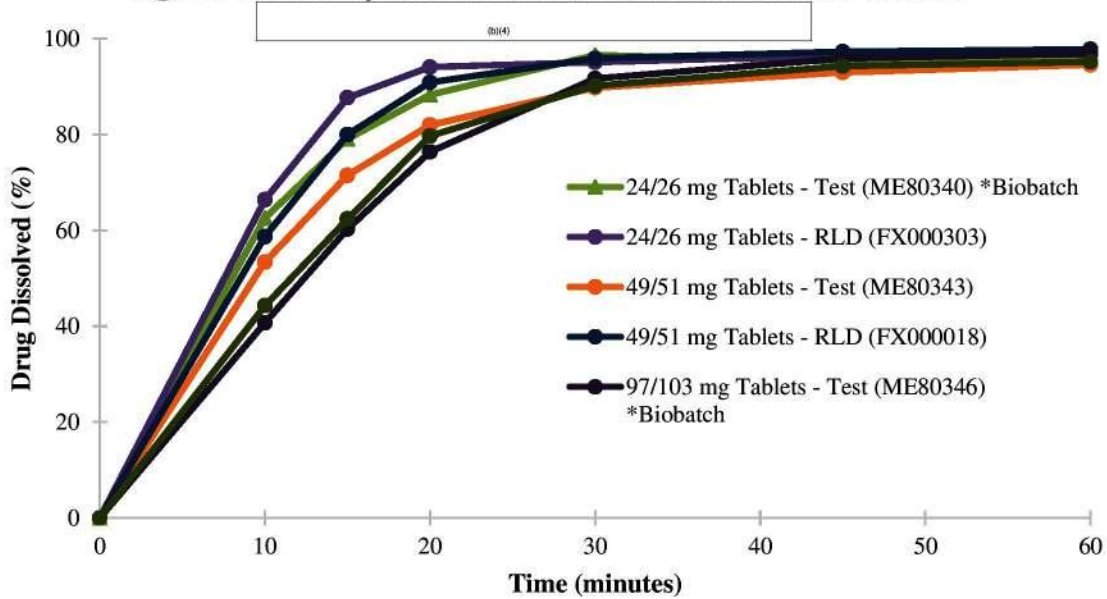
Figure 1. Summary of mean *in vitro* dissolution data for Sacubitril



¹⁰ [Application 213719 - Sequence 0007 - Dissolution Development Report](#)

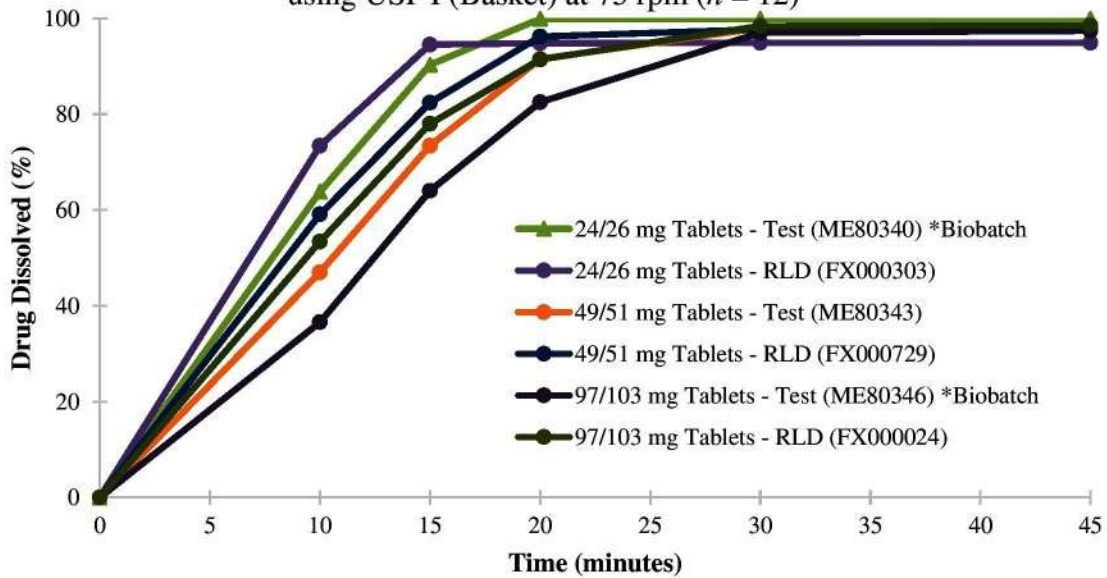
¹¹ [Application 213719 - Sequence 0001 - 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods-pdf](#)

Figure 2. Summary of mean *in vitro* dissolution data for Valsartan



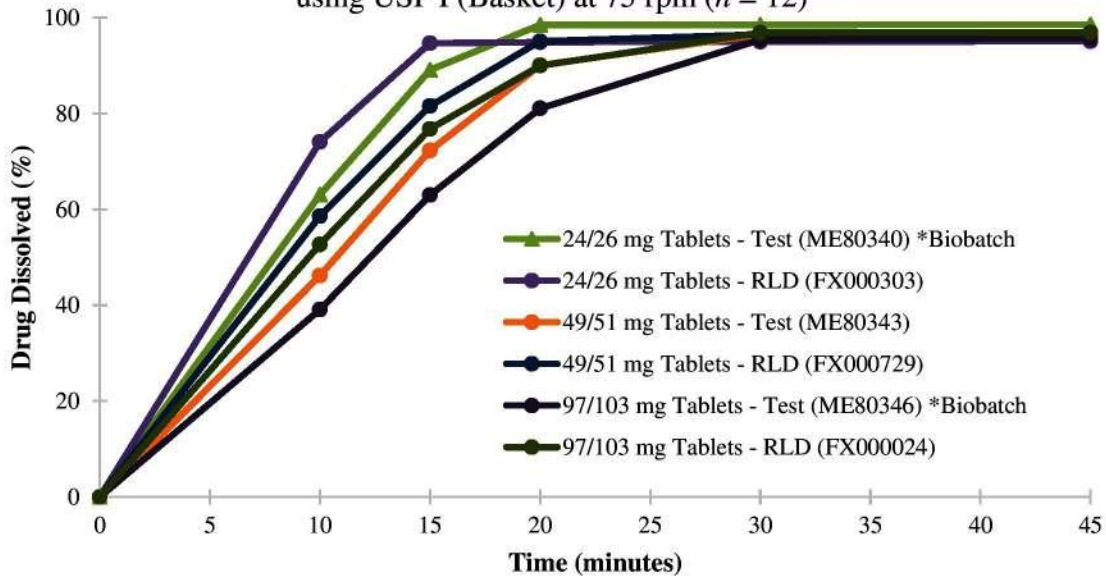
In a response (dated February 24, 2020) to an Information Request, the Applicant adopted the new dissolution method described in the FDA dissolution database [900 mL of pH 6.8 phosphate buffer using USP Apparatus I (Basket) at 75 rpm]. The dissolution data generated from this new dissolution method are shown in Figures 3 and 4.¹²

Figure 3. Summary of mean *in vitro* dissolution data for Sacubitril using USP I (Basket) at 75 rpm (*n* = 12)



¹² [Application 213719 - Sequence 0007 - Individual Unit Dissolution Data](#)

Figure 4. Summary of mean *in vitro* dissolution data for Valsartan using USP I (Basket) at 75 rpm (*n* = 12)



6. **Dissolution Acceptance Criterion:** Based on the totality of the provided information and data, including BE studies on lowest and highest strength and the dissolution data, the proposed acceptance criterion of “NLT % (Q) of Sacubitril and Valsartan in 30 minutes” using the newly proposed dissolution method is adequate for quality control testing of the proposed drug product.
7. **Dissolution in Stability:** The Applicant carried out dissolution stability studies on the exhibit batches in accelerated ($40^{\circ} \pm 2^{\circ}\text{C}/75\% \pm 5\% \text{RH}$) and long-term ($25^{\circ} \pm 2^{\circ}\text{C}/60\% \pm 5\% \text{RH}$) conditions.¹³ No significant changes in dissolution at 45 minutes in stability in both accelerated and long-term conditions up to 6 months were observed using the originally proposed dissolution method. The 12 months old samples stored at long-term conditions also showed rapid dissolution using the newly proposed dissolution method.
8. **Dissolution Risk/Mitigation Assessment:** The Applicant provided information suggest that Sacubitril/Valsartan is considered . However, the information available to the Reviewer indicate that the solubility and the proposed drug product has a relatively short T_{max} , therefore the risk is considered medium to high. The dissolution method and acceptance criteria are set appropriately to mitigate the risk of the change in the drug product performance.

Additional Note: The originally posted dissolution method

(b)(4)

the Applicant proposed dissolution method using USP Type-I basket method at

¹³ [Application 213719 - Sequence 0001 - 3.2.P.8.1 Stability Summary and Conclusion](#)

rotational speed of 75 rpm. This new method was found to be acceptable for the NDA and therefore, [REDACTED]

[REDACTED] (b)(4) the FDA dissolution database was updated with the new dissolution method [900 mL of Phosphate Buffer, pH 6.8 using USP apparatus 1 (basket) at 75 rpm].

[REDACTED] (b)(4) because the formulation is similar to the NDA. Therefore, the Applicant was asked to conduct dissolution testing using the newly posted dissolution method.

Appendix 1: Biopharmaceutics Information Request

The following Biopharmaceutics Information Request (IR) comments were conveyed to the Applicant on December 23, 2019:

1.

(b)(4)

The limited data/information provided are not adequate to demonstrate the suitability/discriminating ability of the proposed dissolution method for your proposed drug product. Please note that the discriminating ability of the dissolution method should be investigated towards the critical material attributes (CMAs), critical process parameters (CPPs) and critical formulation variables (CFVs) which affect dissolution. In general, the testing conducted to demonstrate the discriminating ability of the dissolution method should compare the dissolution profiles of the proposed drug product(target) and the formulations/product that are intentionally manufactured with meaningful variations, i.e., aberrant formulations and manufacturing conditions with $\pm 10-20\%$ change to the specification-ranges of these variables for the most relevant CMA's and CPPs. Submit a separate dissolution method development report.

2. The dissolution data demonstrate that the dissolution of some units of the test product remains incomplete using your proposed method, for example some units of Batch #ME80343

(b)(4) The dissolution profiles of the exhibit batches, including the batch #ME80345, showed (b)(4)

(b)(4) In addition, there are differences between the dissolution profiles between the strengths of the proposed drug product. Explain the root cause of the incomplete dissolution and observed (b)(4) of the proposed drug product using your proposed method. Support your explanation with appropriate data.

3. Note that the FDA dissolution database [https://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_SearchResults.cfm] has been updated with a new dissolution method [900 mL of Phosphate Buffer, pH 6.8 using USP apparatus 1 (basket) at 75 rpm]. Please submit dissolution data [(N=12, individual, mean, CV%)] for all your exhibits batches using this new dissolution method. If the dissolution of your proposed drug product remains incomplete (b)(4) originally proposed dissolution method (b)(4) then you may consider this new FDA database dissolution method (Basket/75 rpm) for the quality control testing of your proposed drug product.

If you choose to follow this new FDA database dissolution method (Basket/75 rpm), then please submit the information/data showing the suitability/discriminating ability of the proposed dissolution method for your proposed drug product, as per above recommendations regarding the demonstration of the suitability/discriminating ability of the method.

The Applicant responded to the above Biopharmaceutics Information Request on February 24, 2020, provided additional dissolution data and information, adopted the new FDA dissolution database method for quality control testing of their proposed drug product, and accordingly updated the drug product release and stability specifications.¹⁴ The response is adequate.

¹⁴ [Application 213719 - Sequence 0007 - 3.2.P.5.1 Specification\(s\)](#)



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Date: 4/06/2020 10:24:53AM
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DIVISION OF BIOEQUIVALENCE ASSESSMENT

ANDA No.	213719		
Drug Product Name	Sacubitril/Valsartan Tablets		
Strength(s)	24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg		
Applicant Name	Zydus Pharmaceuticals (USA) Inc.		
Applicant Address	73-B, Route 31 North Pennington, NJ 08534		
US Contact Name and US Mailing Address	Srinivas Gurram (Srini), VP & Head of RA & QA - North America/ Dhaval N. Desai- Manager, Reg. Affairs 73-B, Route 31 North Pennington, NJ 08534 gsrinivas@zydususa.com		
US Contact Telephone Number	(b)(6)		
US Contact Fax Number	609-730-1999		
Original Submission and Amendment(s) Date(s)	7/8/2019 1/9/2020 (Bioequivalence/Response to Discipline Review Letter) 2/24/2020 (Quality/Response to Discipline Review Letter) (dissolution study)		
Submission Date(s) of Amendment(s) Under Assessment	N/A*		
Primary Assessor	Tian Ma, Ph.D.		
Secondary Assessor	Amanda Jones, Ph.D.		
Tertiary Assessor	N/A		
Study Number(s)	BA18086532	BA17861024-01	BA18086667
Study Type(s)	Fasting	Fed	Fasting (additional)
Strength(s)	97 mg/103 mg	97 mg/103 mg	24 mg/26 mg
Clinical Site	Cliantha Research Limited		
Clinical Site Address	1st floor, Silver Arcade, Near Ashwamegh III, Samrajya, Mujmahuda Road, Akota, Vadodara-390020, Gujarat, India		
Analytical Site	(b)(4)		
Analytical Site Address			
Study Number(s)	BA17861001-01	BA17861002-01	

Study Type(s)	Fasting (pilot)	Fed (pilot)	
Strength(s)	97 mg/103 mg	97 mg/103 mg	
Clinical Site	Clantha Research Limited		
Clinical Site Address	1 st floor, Silver Arcade, Near Ashwamegh III, Samrajya, Mujmahuda Road, Akota, Vadodara-390020, Gujarat, India		
Analytical Site	(b)(4)		
Analytical Site Address			
Office of Study Integrity and Surveillance (OSIS) status	<u>Backlog, Year 1 and Year 2 ANDAs</u> ☐ Pending ☐ Complete ☐ 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 ☐ 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	N/A		
Justification for Major Designation	N/A		
Overall Assessment Result	☒ Adequate ☐ Inadequate		
Product Specific Guidance (PSG) Referenced in Assessment	☒ Recommended/Latest Revision Date: <u>April 2016</u> RLD Number: <u>207620</u> ☐ 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	Fasting	97 mg/ 103 mg	☒ Adequate ☐ Inadequate
1, 6	Fed	97 mg/ 103 mg	☒ Adequate ☐ Inadequate

¹ Requests submitted under 21 CFR 320.22(d)(2) or 320.24(b)(6).

1, 7	Waiver/Deem Bioequivalent	24 mg/26 mg ² and 49 mg/51 mg	☒ Adequate ☐ Inadequate

* The current assignment was made under the 12/28/2020 submission.

1 EXECUTIVE SUMMARY

This is an addendum to the Division of Bioequivalence I (DBI)'s assessment of ANDA 213719 completed on 4/22/2020³. The overall assessment outcome was considered ADEQUATE.

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 allows oral suspension to be substituted at the recommended tablet dosage in patients unable to swallow tablets). This evaluation is in line with the discussions in July 2021 within DBI for this drug product, where it was decided that the test formulation evaluation of suspension prepared using Ora-Plus® and Ora-Sweet® SF should be conducted for ANDAs for this drug product.

Based on the evaluation (please see Section 2 for details), the suspension formulation of the test product is acceptable.

The test formulation remains adequate from bioequivalence perspective.

The application remains **adequate**.

NOTE TO REGULATORY PROJECT MANAGER: The bioequivalence assessment outcome does not change. No letter will be communicated to the applicant as result of this addendum.

There are two Policy Alerts related to this drug product: Citizen Petition (CP) # FDA-2019-P-1893, for ENTRESTO® (sacubitril/valsartan) Tablets and CP FDA-2019-P-2869 for multiple valsartan products or drug products containing valsartan.

No Approval Actions (AP/TA) can be taken prior to contacting Policy Lead. All disciplines can continue communications (CRL, IR/DRL).

² In the original submission, the applicant submitted a pivotal fasting pharmacokinetic (PK) for the 24 mg/26 mg strength. However, since the applicant's new dissolution method is considered acceptable by the biopharmaceutics assessor, and all 3 strengths of the test product using the new dissolution method are dissolving based on the mean dissolution data, this dissolving observation is used to support biowaiver of the lower 2 strengths. Therefore, this fasting study for the 24 mg/26 mg strength is not extensively assessed.

³ GDRP: ANDA-213719-ORIG-1, Bioequivalence Review, A213719N000DB-Review02-DRLResponse01092020.pdf, 4/22/2020.

2 APPENDIX

2.1 Test Formulation⁴

Sr. No.	Name of Ingredient	Quantity per Unit (mg)		% w/w**		Function
		24 mg/26 mg	49 mg/51 mg	24 mg/26 mg	49 mg/51 mg	
1	Sacubitril/Valsartan* [@]	(b)(4)	(b)(4)	(b)(4)	(b)(4)	Active ingredient
2	Microcrystalline Cellulose NF (b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	
3	Low Substituted Hydroxy Propyl Cellulose NF (b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	
4	Colloidal Silicon Dioxide, NF (b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	
5	Sodium Stearyl Fumarate NF	(b)(4)	(b)(4)	(b)(4)	(b)(4)	
Total (Core Tablet)		102.400	204.800	390.000	-	-

(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)

2.3.1 Inactive Ingredients (IIG Table) – Evaluation for Microcrystalline Cellulose

Excipient	From Tablet (49 mg/51 mg strength)*		MDI (mg) from Suspension	Combined MDI (mg) from Tablets and Suspension	FDA's IIG Limit (mg, Route of Administration) ⁶
	Amount (mg)/Tablet	MDI Amount (mg)/Day			
Microcrystalline Cellulose	(b)(4)				
(b)(4)					

Comments on Formulation: Acceptable

- The formulation of the test product, as tablet, was previously evaluated and found acceptable³. 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

⁶ IIG-MDD_Master Spreadsheet: [\fda.gov\wode\CDER\OGD\All\OGDS11\OFFICE OF BIOEQUIVALENCE\Project Management\Kinbo_Lee - IIG-MDD Master Spreadsheet\IIG-MDD_Master Spreadsheet_Final.xls](#)

(b)(4)

perspective,

(b)(4)

(b)(4)

The RLD labeling includes Recommended Dose Titration table (please see table below). From this information, the assessor calculated the maximum daily dose (MDD, see yellow highlighted). Please note that the dose of sacubitril and valsartan is also presented as combination of the two drug components per the RLD labeling. For example, ENTRESTO 800 mg⁹/200 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 included in the last column of the table below.

	Titration Step Dose (twice daily)			MDD*	MDD*
	Starting	Second	Final		(sacubitril+valsartan)
Pediatric Patients Less than 40 kg	1.6 mg/kg	2.3 mg/kg	3.1 mg/kg	6.2 mg/kg	248 mg (40kg patients)
Pediatric Patients At least 40 kg, less than 50 kg	24/26 mg	49/51 mg	72/78 mg	144/156 mg	300 mg
Pediatric Patients At least 50 kg	49/51 mg	72/78 mg	97/103 mg	194/206 mg [^]	400 mg [^]

* Added by the current assessor based on the information in the RLD labeling.

[^] This is also the MDD for adult population.

Per the RLD labeling, to prepare for 200 mL suspension, 60 mL of Ora-Plus® and 140 mL of Ora-Sweet® SF are used.

(b)(4)

(b)(4)

⁸ GDRP: ANDA-213682-ORIG-1-AMEND-11, Bioequivalence Review, A213682N000DB-Review01-Amend11302020.pdf, 7/15/2021.

(b)(4)

(b)(4)

The suspension formulation when prepared using Ora-Plus® and Ora-Sweet® SF does not pose safety concern from the IIG perspective hence is adequate.

- (b)(4)

- The formulation of suspension prepared from the test product is **acceptable**.

NOTE TO REGULATORY PROJECT MANAGER: The bioequivalence assessment outcome does not change. No letter will be communicated to the applicant as result of this addendum.

There are two Policy Alerts related to this drug product: Citizen Petition (CP) # FDA-2019-P-1893, for ENTRESTO® (sacubitril/valsartan) Tablets and CP FDA-2019-P-2869 for multiple valsartan products or drug products containing valsartan.

No Approval Actions (AP/TA) can be taken prior to contacting Policy Lead. All disciplines can continue communications (CRL, IR/DRL).

2.4 Outcome Page

Completed Assignment for 213719 ID: 45882

Reviewer: Ma, Tian

Date

Completed:

Verifier: ,

Date Verified:

Division: Division of Bioequivalence

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

Items:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Score</i>	<i>Subtotal</i>		
45882	1/9/2020	BIO	Addendum [1]	1	1	Edit	Delete
45882	1/9/2020	Parallel	Addendum (not for Clarification or Error Correction) [1]	1	1	Edit	Delete
				Total:	2		

DIVISION OF BIOEQUIVALENCE ASSESSMENT

ANDA No.	213719		
Drug Product Name	Sacubitril/Valsartan Tablets		
Strength(s)	24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg		
Applicant Name	Zydus Pharmaceuticals (USA) Inc.		
Applicant Address	73-B, Route 31 North Pennington, NJ 08534		
US Contact Name and US Mailing Address	Srinivas Gurrum (Srini), VP & Head of RA & QA - North America/ Dhaval N. Desai- Manager, Reg. Affairs 73-B, Route 31 North Pennington, NJ 08534 grrinivas@zydususa.com		
US Contact Telephone Number	(b)(6)		
US Contact Fax Number	609-730-1999		
Original Submission Date(s)	7/8/2019		
Submission Date(s) of Amendment(s) Under Assessment	1/9/2020 (Bioequivalence/Response to Discipline Review Letter) 2/24/2020 (Quality/Response to Discipline Review Letter) (dissolution study)		
Primary Assessor	Tian Ma, Ph.D.		
Secondary Assessor	Amanda Jones, Ph.D.		
Tertiary Assessor	N/A		
Study Number(s)	BA18086532	BA17861024-01	BA18086667
Study Type(s)	Fasting	Fed	Fasting (additional)
Strength(s)	97 mg/103 mg	97 mg/103 mg	24 mg/26 mg
Clinical Site	Cliantha Research Limited		
Clinical Site Address	1st floor, Silver Arcade, Near Ashwamegh III, Samrajya, Mujmahuda Road, Akota, Vadodara-390020, Gujarat, India		
Analytical Site	(b)(4)		
Analytical Site Address			
Study Number(s)	BA17861001-01	BA17861002-01	
Study Type(s)	Fasting (pilot)	Fed (pilot)	
Strength(s)	97 mg/103 mg	97 mg/103 mg	

Clinical Site	Cliantha Research Limited		
Clinical Site Address	1 st floor, Silver Arcade, Near Ashwamegh III, Samrajya, Mujmahuda Road, Akota, Vadodara-390020, Gujarat, India		
Analytical Site	(b)(4)		
Analytical Site Address			
Office of Study Integrity and Surveillance (OSIS) status	<u>Backlog, Year 1 and Year 2 ANDAs</u> ☐ Pending ☐ Complete ☐ 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 ☐ 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	N/A		
Justification for Major Designation	N/A		
Overall Assessment Result	☒ Adequate ☐ Inadequate		
Product Specific Guidance (PSG) Referenced in Assessment	☒ Recommended/Latest Revision Date: <u>April 2016</u> <u>RLD Number: 207620</u> ☐ 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	Fasting	97 mg/ 103 mg	☒ Adequate ☐ Inadequate
1, 6	Fed	97 mg/ 103 mg	☒ Adequate ☐ Inadequate

¹ Requests submitted under 21 CFR 320.22(d)(2) or 320.24(b)(6).

1, 7	Waiver/Deem Bioequivalent	24 mg/26 mg ² and 49 mg/51 mg	☒ Adequate ☐ Inadequate

1 EXECUTIVE SUMMARY

This is assessment of an amendment.

The original application submitted on 7/8/2019 contained the results of fasting and fed bioequivalence (BE) studies comparing a test product Zydus Pharmaceuticals (USA) Inc.'s Sacubitril/Valsartan Tablets, 97 mg/103 mg to the corresponding reference product Novartis Pharmaceuticals Corp's Entresto® (sacubitril/valsartan) Tablets, 97 mg/103 mg. The fasting BE study was designed as a single-dose, two-treatment, two-sequence, four-period, fully replicated study in healthy male subjects, and the fed BE study was designed as a single-dose, two-way crossover study in healthy male subjects. In the original BE assessment³, the applicant's fasting and fed BE studies were found incomplete due to bioanalytical deficiencies (for both fasting and fed studies) and incomplete dataset (for fasting study only). In addition, the applicant's dissolution testing data for the 2 lower strengths (24 mg/26 mg and 49 mg/51 mg strengths) were found incomplete to support biowaiver of these 2 strengths due to deficiencies in dissolution method^{4,5}.

In the current amendment submitted on 1/9/2020, the applicant adequately addressed the deficiencies. The fasting and fed BE studies are now acceptable. The assessor's results for the fasting study⁶ are summarized in the tables below.

² In the original submission, the applicant submitted a pivotal fasting pharmacokinetic (PK) for the 24 mg/26 mg strength. However, since the applicant's new dissolution method is considered acceptable by the biopharmaceutics assessor, and all 3 strengths of the test product using the new dissolution method are rapidly dissolving based on the mean dissolution data, this rapidly dissolving observation is used to support biowaiver of the lower 2 strengths. Therefore, this fasting study for the 24 mg/26 mg strength is not extensively assessed.

³ GDRP: ANDA-213719-ORIG-1, Bioequivalence Review, A213719N000DB-Review01-07082019.docx, 12/22/2019.

⁴ GDRP: ANDA-213719-ORIG-1, Biopharmaceutics Review, A213719 Biopharm R01.IQ.docx, 12/11/2019. This assessment appears to be currently removed from GDRP, but its previous existence could still be traced by the task updates in GDRP: ANDA-213719-ORIG-1, Biopharmaceutics Review, Updates tab.

⁵ GDRP: ANDA-213719-ORIG-1, Send DRL, A213719 DRL.docx, 12/23/2019 (p. 4 of 7).

⁶ The assessor's results for the fed study are provided in the original BE assessment.

Sacubitril and Valsartan Tablets, 97 mg/ 103 mg 1 x 97 mg/ 103 mg Fasting Bioequivalence Study No. BA18086532, N=34 (Male=34 and Female=0) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Sacubitril					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (hr *µg/ml)	2.63	2.66	0.99	96.28	101.59
AUC _∞ (hr *µg/ml)	2.66	2.68	0.99	96.43	101.76
C _{max} (µg/ml)	1.97	1.99	0.99	88.84	110.74
Valsartan					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (hr *µg/ml)	32.10	32.02	1.00	91.63	109.71
AUC _∞ (hr *µg/ml)	32.67	32.58	1.00	91.82	109.53
C _{max} (µg/ml)	5.18	5.01	1.03	94.68	113.07

Fasting Bioequivalence Study No. BA18086532								
Sacubitril								
Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s _{2wr}	s _{WR}	Criteria Bound	Method Used	Outcome
LAUC _t	0.99	96.28	101.59	0.0077996	0.0883151	-0.003552	Unscaled	PASS
LAUC _i	0.99	96.43	101.76	0.0075405	0.0868362	-0.003491	Unscaled	PASS
LC _{max}	0.97	88.84	110.74	0.1338316	0.3658301	-0.067214	Scaled/PE	PASS
Valsartan								
Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s _{2wr}	s _{WR}	Criteria Bound	Method Used	Outcome
LAUC _t	1.00	91.63	109.71	0.104886	0.3238611	-0.05488	Scaled/PE	PASS
LAUC _i	1.00	91.82	109.53	0.1016638	0.3188476	-0.053263	Scaled/PE	PASS
LC _{max}	1.03	94.68	113.07	0.1291397	0.3593602	-0.065172	Scaled/PE	PASS

Formulation

According to Office of Pharmaceutical Quality (OPQ)'s 12/23/2019 Discipline Review Letter (DRL), (b)(4)

(b)(4)

(b)(4) In the current submission, the applicant provided the updated components and composition table, (b)(4)

(b)(4) The updated formulations of the test product remain acceptable for all 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg strengths. The

24 mg/26 mg and 49 mg/51 mg strengths of the test product remain proportionally similar to the bio-strength (97 mg/103 mg) based on the updated formulation table.

It is noted that the applicant did not change formulation, but rather corrected the incorrect information in the original formulation table. In addition, according to the current draft of the Drug Product assessment (not yet finalized)⁷, the drug product assessor states that the exhibit batches met the drug product release specification. Therefore, the assessor does not consider it necessary for the applicant to conduct bridging studies due to the updated formulation table.

In vitro comparative dissolution study

In response to the biopharmaceuticals' 12/23/2019 DRL deficiency regarding the applicant's original dissolution method [REDACTED]

[REDACTED] the applicant re-conducted dissolution study using the current FDA-recommended method (900 mL of pH 6.8 phosphate buffer using *USP Apparatus I* at 75 rpm). This new dissolution method is considered acceptable per the biopharmaceuticals amendment assessment⁸. The new dissolution testing data for the 24 mg/26 mg and 49 mg/51 mg strengths are acceptable to support waiver request of these 2 strengths.

As a result, the Division of Bioequivalence I (DBI) **grants** the biowaiver for *in vivo* BE study requirements for 24 mg/26 mg and 49 mg/51 mg strengths based on criteria set forth in 21 CFR § 320.22 (d)(2).

The application is **acceptable** with no deficiencies.

NOTE TO DBI PROJECT MANAGER and REGULATORY PROJECT MANAGER (RPM): As per OGD Policy, two Citizen Petitions (CPs) are pending for this drug product which state the following:

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

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

Citizen petition (FDA-2019-P-2869) for Multiple drug products containing valsartan, which requests FDA to: 1) review and significantly lower the acceptable intake/permitted

⁷ GDRP: ANDA-213719-ORIG-1, Drug Product Review, ANDA 213719 IQA_DS DP LBL 0001.docx, 4/2/2020. It is noted that this drug product assessment draft is not yet finalized.

⁸ GDRP: ANDA-213719-ORIG-1, Biopharmaceuticals Review, A13719 Biopharm R01-AQ.docx, 4/3/2020.

daily exposure limit of DMF, as listed in the current FDA guidance Q3C – Tables and List, Guidance for Industry, from its current level of 8,800,000 nanograms to less than 1,000 nanograms (and potentially as low as 96 nanograms); 2) request a recall of identified lots of valsartan on the basis that, due to contamination with a probable human carcinogen, these drugs are adulterated under Section 501 of the FDCA (21 U.S.C. § 351) and misbranded under Section 502 of the FDCA (21 U.S.C. § 352); 3) conduct examinations and investigation under Section 702 (a) of the FDCA (21 U.S.C. § 372(a)) regarding these products, their manufacturing processes, and the manufacturer submissions made for FDA approval under 704 (a) of the FDCA (21 U.S.C. § 374(a)) and effect labeling revisions as needed.

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

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3 SUBMISSION SUMMARY

Pharmacokinetic (PK) Bioequivalence (BE) Studies

Deficiency Related to Pre-Study Method Validation

3.1 Deficiency Comment #1

Please specify what anticoagulant was used in Addendum-I of your method validation AP LC/MS/MS 528.MV.001 (7/8/2019 submission, Module 5.3.1.4 BA17861024-01...\attachment-6-2-addendum-1-method-val-reports).

Applicant's Response to Deficiency Comment #1:

We wish to inform the Agency that, in Addendum-I of our method validation AP LC/MS/MS 528.MV.001 provided in the original submission (eCTD sequence# 0001), the following experiments were performed:

- *Carryover*
- *Selectivity*
- *P & A batch*

In the Selectivity experiment, blank human plasma (having K2-EDTA as an anticoagulant) was screened and the screened plasma was used for other experiments (i.e., Carryover and P & A batch experiments).

*We have provided the **raw data of blank (Zero) matrix receipt record and sample retrieval and re-storage form** in Module 5.3.1.4 of this amendment.*

Assessor's Comments:

According to the original BE assessment³, the applicant conducted method validation addendum to support change in analytical site in the company from the one used in the method validation to the one used in the fasting and fed studies. However, it was unclear what anticoagulant was used in this method validation addendum. In the current submission, the applicant stated that K2EDTA was used as the anti-coagulant in method validation addendum. This is the same anti-coagulant used in the applicant's method validation as well as fasting and fed studies.

The applicant's response is **acceptable**.

Deficiency Related to Fasting Study BA18086532

3.2 Deficiency Comment #2

The Agency acknowledges that you provided SAS .xpt datasets for subjects that completed all 4 periods of the study (7/8/2019 submission, Module 5.3.1.2. BA18086532...\Data

Analysis Data\Analysis Dataset Legacy\pk-sacubitril.xpt, \raw-sacubitril.xpt, \pk-valsartan.xpt, and \raw-valsartan/xpt). Please update your SAS .xpt datasets to also include data from all discontinued subjects (i.e., Subjects)

Applicant’s Response to Deficiency Comment #2:

As recommended by the Agency, the SAS.xpt dataset files are updated to include data from all discontinued subjects [i.e., Subjects (Period-I & II), (Period-I), (Period-I & II), (Period-I & II), (Period-I & II), (Period-I), (Period-I & II), (Period-I & II), (Period-I) and (Period-I)].

*The revised **define-sacubitril.pdf**, **define-valsartan.pdf**, **pk-sacubitril.xpt**, **pk-valsartan.xpt**, **raw-sacubitril.xpt**, and **raw-valsartan.xpt** are provided in Module 5.3.1.2 of this amendment.*

Assessor’s Comments:

As mentioned in the original BE assessment³, the applicant only provided SAS .xpt dataset for subjects that completed all 4 periods of the study, in accordance with their protocol. The applicant was asked to update the SAS .xpt dataset to also include data from all discontinued subjects. In the current submission, the applicant provided the requested SAS .xpt datasets.

The applicant’s response is **acceptable**.

With the datasets provided, the assessor conducted statistical analysis for the fasting study (#BA18086532) (please see Section 4.1.1.1 for details).

3.3 Other Comments – Updated Formulation Table

It is noted that in OPQ’s DRL dated 12/23/2019⁹, Drug Product assessor issued, among others, the following deficiency:

(b)(4)

(b)(4)

⁹ GDRP: ANDA-213719-ORIG-1, Send DRL, A213719 DRL.docx, 12/23/2019 (p. 2 of 7, Drug Product Deficiency #1).

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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.

Table 9: Comparative composition of all strengths

Sr. No	Name of Ingredient	Quantity/ Tablet (mg)
(b)(4)	(b)(4)	(b)(4)
	Sacubitril/Valsartan*®	24 mg/ 26 mg
	Microcrystalline cellulose	49 mg/ 51 mg
	Low-substituted hydroxypropyl cellulose	97 mg/ 103 mg
	Colloidal silicon dioxide	(b)(4)
	Sodium stearyl fumarate	(b)(4)
	(b)(4)	(b)(4)
	Crospovidone	(b)(4)
	(b)(4)	(b)(4)
	Total (Core Tablet)	102.400 204.800 390.000

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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)

(b)(4) Therefore, the assessor does not consider it necessary for the applicant to conduct bridging studies due to the updated formulation table.

3.4 Other Comments – New Dissolution Study

In response to biopharmaceutics' deficiency⁵ regarding the applicant's original dissolution method (b)(4) the applicant re-conducted dissolution study using the current FDA-recommended method (900 mL of pH 6.8 phosphate buffer using *USP Apparatus I at 75 rpm*). This new dissolution method is considered acceptable per the biopharmaceutics amendment assessment¹⁰. As detailed in Section 4.3, the applicant's new dissolution studies are acceptable to support biowaiver for the 24 mg/26 mg and 49 mg/51 mg strengths of the test product.

¹⁰ GDRP: ANDA-213719-ORIG-1, Biopharmaceutics Review, A13719 Biopharm R01-AQ.docx, 4/3/2020.

4 APPENDIX

4.1 Individual Study Assessments

4.1.1 Single-Dose Fasting Bioequivalence Study

4.1.1.1 Pharmacokinetic Results

4.1.1.1.1 Arithmetic Mean Pharmacokinetic Parameters – Applicant Calculated

Sacubitril

PARAMETER	Test Product: Sacubitril / Valsartan Tablets 97 mg /103 mg		Reference Product: Entresto™ (Sacubitril / Valsartan) Tablet 97 mg/103 mg	
	N	Arithmetic mean ±Std Deviation (Coeff of Variation (%))	N	Arithmetic mean ±Std Deviation (Coeff of Variation (%))
Cmax (µg/ mL)	48	2.061 ± 1.039 (50.410)	48	2.111 ± 1.019 (48.261)
AUCt (µg/mL)*(hr)	48	2.574 ± 0.697 (27.094)	48	2.590 ± 0.615 (23.756)
AUCi (µg/mL)*(hr)	48	2.602 ± 0.693 (26.650)	48	2.616 ± 0.613 (23.416)
AUC_%Extrap_obs	48	1.174 ± 1.428 (121.671)	48	1.070 ± 1.299 (121.350)
Kel (1/hr)	48	0.948 ± 0.247 (26.067)	48	0.948 ± 0.295 (31.114)
tHalf (hr)	48	0.793 ± 0.269 (33.942)	48	0.816 ± 0.341 (41.787)
Tmax (hr)*	48	0.500 (0.333 - 2.667)	48	0.667 (0.167- 4.000)

* Tmax values are presented as median (range)

Valsartan

PARAMETER	Test Product: Sacubitril / Valsartan Tablets 97 mg /103 mg		Reference Product: Entresto™ (Sacubitril / Valsartan) Tablet 97 mg/103 mg	
	N	Arithmetic mean ±Std Deviation (Coeff of Variation (%))	N	Arithmetic mean ±Std Deviation (Coeff of Variation (%))
Cmax (µg/ mL)	48	5.440 ± 1.952 (35.879)	48	5.247 ± 1.881 (35.855)
AUCt (µg/mL)*(hr)	48	33.963 ± 13.579 (39.983)	48	33.511 ± 11.881 (35.455)
AUCi (µg/mL)*(hr)	48	34.542 ± 13.999 (40.527)	48	34.052 ± 12.172 (35.746)
AUC_%Extrap_obs	48	1.589 ± 0.991 (62.365)	48	1.578 ± 1.169 (74.076)
Kel (1/hr)	48	0.092 ± 0.026 (28.242)	48	0.096 ± 0.027 (27.810)
tHalf (hr)	48	8.091 ± 2.305 (28.489)	48	7.736 ± 2.198 (28.408)
Tmax (hr)*	48	1.750 (1.250 - 4.000)	48	1.750 (1.000- 5.000)

* Tmax values are presented as median (range)

4.1.1.1.2 Arithmetic Mean Pharmacokinetic Parameters – Assessor’s Results

Sacubitril

Replicate 1 (Periods 1 and 2)

Parameter	Unit	Test				Reference				Ratio (T/R)
		Mean	CV%	Min	Max	Mean	CV%	Min	Max	
AUCT	ug hr/mL	2.701	28.00	1.71	4.49	2.635	26.87	1.60	4.42	1.02
AUCINF	ug hr/mL	2.735	27.32	1.77	4.51	2.657	26.51	1.62	4.45	1.03
C _{MAX}	ug/mL	2.223	41.31	1.00	4.49	2.020	45.26	0.73	5.03	1.10
T _{MAX}	hr	0.500	.	0.33	1.50	0.500	.	0.33	4.00	1.00
KEL	hr ⁻¹	0.935	26.36	0.44	1.56	0.901	27.13	0.34	1.37	1.04
THALF	hr	0.892	37.49	0.46	2.03	0.773	18.00	0.48	1.10	1.15

* 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	ug hr/mL	2.589	27.70	1.59	4.53	2.654	21.61	1.80	4.43	0.98
AUCINF	ug hr/mL	2.608	27.57	1.60	4.55	2.684	21.46	1.82	4.45	0.97
C _{MAX}	ug/mL	2.020	56.62	0.58	6.06	2.280	46.61	0.95	4.26	0.89
T _{MAX}	hr	0.500	.	0.33	2.67	0.667	.	0.17	3.50	0.75
KEL	hr ⁻¹	0.937	38.86	0.27	1.89	0.955	20.40	0.66	1.42	0.98
THALF	hr	0.737	24.36	0.44	1.31	0.850	51.82	0.37	2.54	0.87

* 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	ug hr/mL	2.653	27.72	1.59	4.53	2.644	24.52	1.60	4.43	1.00
AUCINF	ug hr/mL	2.681	27.29	1.60	4.55	2.668	24.25	1.62	4.45	1.00
C _{MAX}	ug/mL	2.136	47.57	0.58	6.06	2.132	45.98	0.73	5.03	1.00
T _{MAX}	hr	0.500	.	0.33	2.67	0.584	.	0.17	4.00	0.86
KEL	hr ⁻¹	0.936	32.00	0.27	1.89	0.924	24.26	0.34	1.42	1.01
THALF	hr	0.825	34.78	0.44	2.03	0.806	37.95	0.37	2.54	1.02

* T_{max} values are presented as median, range.

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Valsartan

Replicate 1 (Periods 1 and 2)

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	ug hr/mL	34.187	39.64	11.55	74.99	34.664	34.01	12.36	67.38	0.99
AUCINF	ug hr/mL	34.762	40.28	12.08	77.60	35.273	34.83	12.60	68.67	0.99
C _{MAX}	ug/mL	5.471	32.24	1.93	11.10	5.342	31.65	2.32	11.10	1.02
T _{MAX}	hr	1.625	.	1.25	3.50	2.000	.	1.00	5.00	0.81
KEL	hr-1	0.090	25.51	0.04	0.16	0.083	29.14	0.03	0.17	1.08
THALF	hr	8.371	25.88	4.18	14.39	8.463	31.03	4.24	18.87	0.99

* T_{max} values are presented as median, range.

Replicate 2 (Periods 3 and 4)

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	ug hr/mL	34.322	37.65	10.46	71.52	32.697	35.74	6.88	64.25	1.05
AUCINF	ug hr/mL	35.001	37.75	10.74	72.63	33.255	35.17	7.25	64.78	1.05
C _{MAX}	ug/mL	5.453	37.69	1.76	12.79	5.209	38.18	1.18	10.85	1.05
T _{MAX}	hr	2.000	.	1.25	4.00	1.750	.	1.25	4.00	1.14
KEL	hr-1	0.084	22.18	0.04	0.13	0.091	29.20	0.04	0.16	0.93
THALF	hr	9.128	35.51	5.02	19.93	8.502	29.06	6.34	17.17	1.07

* T_{max} values are presented as median, range.

All Periods (Periods 1, 2, 3 and 4)

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	ug hr/mL	34.245	38.44	10.46	74.99	33.821	34.53	6.88	67.38	1.01
AUCINF	ug hr/mL	34.864	38.86	10.74	77.60	34.408	34.79	7.25	68.67	1.01
C _{MAX}	ug/mL	5.463	34.34	1.76	12.79	5.285	34.21	1.18	11.10	1.03
T _{MAX}	hr	1.750	.	1.25	4.00	1.750	.	1.00	5.00	1.00
KEL	hr-1	0.087	24.28	0.04	0.16	0.086	29.21	0.03	0.17	1.01
THALF	hr	8.696	30.82	4.18	19.93	8.480	29.93	4.24	18.87	1.03

* T_{max} values are presented as median, range.

4.1.1.1.3 Geometric Means and 90% Confidence Intervals – Applicant Calculated

Sacubitril and Valsartan Tablets, 97 mg/ 103 mg 1 x 97 mg/ 103 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasting Bioequivalence Study No. BA18086532							
Sacubitril							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
AUC _{0-t} (hr *µg/ml)	2.491	48	2.523	48	0.9872	95.78	101.75
AUC _∞ (hr *µg/ml)	2.521	48	2.551	48	0.9882	95.88	101.85
C _{max} (µg/ml)	1.850	48	1.898	48	0.9745	NA	NA
Valsartan							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
AUC _{0-t} (hr *µg/ml)	31.441	48	31.454	48	0.9996	NA	NA
AUC _∞ (hr *µg/ml)	31.951	48	31.960	48	0.9997	NA	NA
C _{max} (µg/ml)	5.099	48	4.930	48	1.0343	NA	NA

Fasting Bioequivalence Study No. BA18086532								
Sacubitril								
Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s _{2wr}	s _{WR}	Criteria Bound	Method Used	Outcome
LAUC _t	NA	95.78%	101.75%	0.0078	0.088	NA	Average Bioequivalence	Bioequivalent
LAUC _i	NA	95.88%	101.85%	0.0077	0.088	NA	Average Bioequivalence	Bioequivalent
LC _{max}	0.97	NA	NA	0.1338	0.366	-0.0672	Scaled Average Bioequivalence	Bioequivalent
Valsartan								
Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s _{2wr}	s _{WR}	Criteria Bound	Method Used	Outcome
LAUC _t	1.00	NA	NA	0.1056	0.325	-0.0553	Scaled Average Bioequivalence	Bioequivalent
LAUC _i	1.00	NA	NA	0.1032	0.321	-0.0541	Scaled Average Bioequivalence	Bioequivalent
LC _{max}	1.03	NA	NA	0.1291	0.359	-0.0652	Scaled Average Bioequivalence	Bioequivalent

4.1.1.1.4 Geometric Means and 90% Confidence Intervals – Assessor Calculated

Sacubitril and Valsartan Tablets, 97 mg/ 103 mg 1 x 97 mg/ 103 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasting Bioequivalence Study No. BA18086532							
Sacubitril							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
AUC _{0-t} (hr *µg/ml)	2.63	54	2.66	54	0.99	96.28	101.59
AUC _∞ (hr *µg/ml)	2.66	54	2.68	54	0.99	96.43	101.76
C _{max} (µg/ml)	1.97	54	1.99	54	0.99	88.84	110.74
Valsartan							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
AUC _{0-t} (hr *µg/ml)	32.10	54	32.02	54	1.00	91.63	109.71
AUC _∞ (hr *µg/ml)	32.67	54	32.58	54	1.00	91.82	109.53
C _{max} (µg/ml)	5.18	54	5.01	54	1.03	94.68	113.07

Fasting Bioequivalence Study No. BA18086532								
Sacubitril								
Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	Outcome
LAUC _t	0.99	96.28	101.59	0.0077996	0.0883151	-0.003552	Unscaled	PASS
LAUC _i	0.99	96.43	101.76	0.0075405	0.0868362	-0.003491	Unscaled	PASS
LC _{max}	0.97	88.84	110.74	0.1338316	0.3658301	-0.067214	Scaled/PE	PASS
Valsartan								
Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	Outcome
LAUC _t	1.00	91.63	109.71	0.104886	0.3238611	-0.05488	Scaled/PE	PASS
LAUC _i	1.00	91.82	109.53	0.1016638	0.3188476	-0.053263	Scaled/PE	PASS
LC _{max}	1.03	94.68	113.07	0.1291397	0.3593602	-0.065172	Scaled/PE	PASS

4.1.1.1.5 Additional Information for the Study

Sacubitril

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).	☐ Yes ☒ No Please see assessor's comments below
Were the subjects dosed in groups?	☐ Yes ☒ No

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If yes, was the statistical analysis proper? Is reanalysis by assessor necessary?	
Are there measurable drug concentrations at 0 hr? If yes, please comment (and take necessary action, if needed).	☐ Yes ☒ No
Are there first measurable drug concentration as Cmax? If yes, please comment.	☒ Yes ☐ No Please see assessor's comments below
Are there Cmax at the first time point? If yes, is the study (sample) design adequate?	☒ Yes ☐ No Please see assessor's comments below

Ratio of AUC _{0-t} /AUC _∞				
Treatment	n [#]	Mean	Minimum	Maximum
Test	56	0.99	0.90	1.00
Reference	56	0.99	0.92	1.00
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below.				N/A

"n" refers to the number of observations.

Valsartan

Is there a Tmax difference between Test and Reference? If yes, please provide brief explanation (or detailed explanation, including Tmax analysis, for substantial difference).	☐ Yes ☒ No Please see assessor's comments below
Were the subjects dosed in groups? If yes, was the statistical analysis proper? Is reanalysis by assessor necessary?	☐ Yes ☒ No
Are there measurable drug concentrations at 0 hr? If yes, please comment (and take necessary action, if needed).	☐ Yes ☒ No
Are there first measurable drug concentration as Cmax? If yes, please comment.	☐ Yes ☒ No
Are there Cmax at the first time point? If yes, is the study (sample) design adequate?	☐ Yes ☒ No

Ratio of AUC _{0-t} /AUC _∞				
Treatment	n [#]	Mean	Minimum	Maximum
Test	56	0.98	0.90	0.99
Reference	56	0.98	0.92	0.99
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below.				N/A

"n" refers to the number of observations.

Comments on PK results: Adequate

- As mentioned in the original BE assessment³, the applicant’s analysis is only based on subjects that completed all 4 periods of the study, in accordance with their protocol. Therefore, the following subjects were not included in the applicant’s analysis. According to DBI’s statistics expert, the Agency’s SAS code for reference scale uses MIXED model for reference-scaled analysis and data from only one T or one R can be included for BE analysis. Therefore, the applicant was asked to provide updated SAS .xpt dataset with the following subjects included.

Subject	Period Completed	Completed Treatment
001	1,2	R,T
	1	T
	1,2	R,T
	1,2	T,R
	1,2	T,R
	1	R
	1,2	T,R
	1,2	R,T
	1	R
	1	T

In the current submission, the applicant provided the requested dataset. With this updated dataset, the assessor conducted statistical analysis using all subjects in the study. In addition, for the assessor’s analysis, the assessor specified linear range used to calculate Kel; therefore, SAS code CALKE was first used to calculate PK parameters for all subject periods. Based on assessor’s CALKE output for PK parameters, the HV-RefScale4Period-ver1 SAS code was then used for statistical analysis (please see assessor’s summary tables above).

- The scaled-average bioequivalence approach is used when the estimated within subject variability (s_{WR}) > 0.294 (i.e. when the s^2_{WR} > 0.086436). In order to be considered bioequivalent to the reference product, the test product must pass the following two conditions¹¹:
 - A 95% upper confidence bound for $(\mu_T - \mu_R)^2 / s^2_{WR}$ determined in a BE study must be $\leq \theta$, or equivalently, a 95% upper confidence bound for $(\mu_T - \mu_R)^2 - \theta s^2_{WR}$ must be ≤ 0 , where s_{WR} is within reference standard deviation determined in the BE study.
 - The point estimate (test/reference geometric mean ratio) must fall within [0.80, 1.25].

¹¹ 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.

For AUC_t and AUC_i of sacubitril, since their corresponding *s*_{WR} are < 0.294, unscaled BE approach is used. Unscaled statistical calculation using HV-RefScale4Period-ver1 SAS code shows that the 90% confidence intervals for AUC_t and AUC_i of sacubitril are within the acceptable limits of 80.00%-125.00%.

For C_{max} of sacubitril as well as AUC_t, AUC_i and C_{max} of valsartan, since their corresponding *s*_{WR} are > 0.294, scaled-average bioequivalence approach is used. Scaled statistical calculation using HV-RefScale4Period-ver1 SAS code shows that the 95% upper confidence bounds for $(\mu_T - \mu_R)^2 - \theta s^2_{WR}$ for these parameters are less than 0, which meet the first condition mentioned above. In addition, the point estimate (test/reference geometric mean ratio) for these parameters are within [0.80, 1.25], which meet the second condition mentioned above. Therefore, the C_{max} of sacubitril as well as AUC_t, AUC_i and C_{max} of valsartan meet the BE criteria for reference-scaled approach.

- The assessor also conducted exploratory statistical analysis only using subjects that completed all 4 periods of the study, as specified in the applicant's protocol. It is noted that excluding subjects that did not complete all 4 periods of the study does not change the study outcome (please see tables below).

Excluding Subjects (Subjects [redacted] That Did Not Complete All 4 Periods of The Study

Parameter	Geometric Means			90% CI	
	Test	Reference	T/R Ratio	Lower CI	Upper CI
Sacubitril					
LAUCT	2.49	2.52	0.99	95.78	101.75
LAUCI	2.52	2.55	0.99	95.94	101.93
LCMAX	1.85	1.90	0.97	86.55	109.72
Valsartan					
LAUCT	31.44	31.49	1.00	90.37	110.35
LAUCI	32.04	32.06	1.00	90.63	110.18
LCMAX	5.10	4.93	1.03	93.68	114.19

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s _{2WR}	s _{WR}	Criteria Bound	Method Used	OUTCOME
Sacubitril								
LAUCT	0.99	95.78	101.75	0.0077996	0.0883151	-0.003552	Unscaled	PASS
LAUCI	0.99	95.94	101.93	0.0075405	0.0868362	-0.003491	Unscaled	PASS
LCMAX	0.97	86.55	109.72	0.1338316	0.3658301	-0.067214	Scaled/PE	PASS
Valsartan								
LAUCT	1.00	90.37	110.35	0.104886	0.3238611	-0.05488	Scaled/PE	PASS
LAUCI	1.00	90.63	110.18	0.1016638	0.3188476	-0.053263	Scaled/PE	PASS
LCMAX	1.03	93.68	114.19	0.1291397	0.3593602	-0.065172	Scaled/PE	PASS

- As mentioned in the original BE assessment³, for sacubitril, 1 subject period (Subject [redacted] Period 3) for the reference product had the first measurable drug concentration as C_{max}, and also first post-dose time point as C_{max}. Based on the

updated SAS .xpt dataset, no additional subject period has first time point C_{max}, or first measurable drug concentration as C_{max}. It should be noted that the applicant included sufficient PK sampling times to cover the expected T_{max} range per the RLD labeling (i.e. 0.5 hr and 1.5 hrs for sacubitril and valsartan, respectively). The applicant included early time point (10 minutes) in addition to 5 more time points within the first hour. This time point selection is in line with *Draft Guidance for Industry – Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted under an ANDA* (posted Dec 2013).

- T_{max} (hr) for the test and reference products, based on assessor's results, are summarized below:

Sacubitril

	Test	Reference	Ratio
Median	0.50	0.584	0.86
Min	0.33	0.17	1.94
Max	2.67	4.00	0.67

Valsartan

	Test	Reference	Ratio
Median	1.75	1.75	1.00
Min	1.25	1.00	1.25
Max	4.00	5.00	0.80

The assessor considers the T_{max} between the test and reference treatment comparable for sacubitril and valsartan.

4.1.1.2 Overall Comment

Was the fasting bioequivalence study acceptable? Adequate

Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study – Assessor’s Results

Sacubitril					
Time (hr)	Test (n= 56)		Reference (n= 56)		T/R Ratio
	Mean (ug/mL)	% CV	Mean (ug/mL)	% CV	
0	0.00	.	0.00	.	-
0.167	0.18	151.94	0.22	246.46	0.82
0.333	1.37	69.44	1.33	70.66	1.03
0.5	1.88	54.60	1.72	55.39	1.09
0.667	1.69	58.71	1.66	59.18	1.02
0.833	1.36	51.55	1.42	58.30	0.96
1	1.11	50.73	1.15	57.29	0.97
1.25	0.86	53.67	0.86	57.21	1.00
1.5	0.69	58.80	0.66	63.24	1.05
1.75	0.53	62.23	0.53	66.84	1.00
2	0.40	58.55	0.41	68.85	0.98
2.333	0.30	69.00	0.30	73.37	1.00
2.667	0.30	82.98	0.27	70.85	1.11
3	0.29	91.64	0.26	94.97	1.12
3.5	0.26	87.77	0.25	109.36	1.04
4	0.20	92.12	0.21	121.63	0.95
5	0.08	88.88	0.10	129.57	0.80
6	0.03	86.33	0.03	118.91	1.00
8	0.00	220.52	0.01	216.62	0.00
10	0.00	-	0.00	-	-
12	0.00	-	0.00	-	-

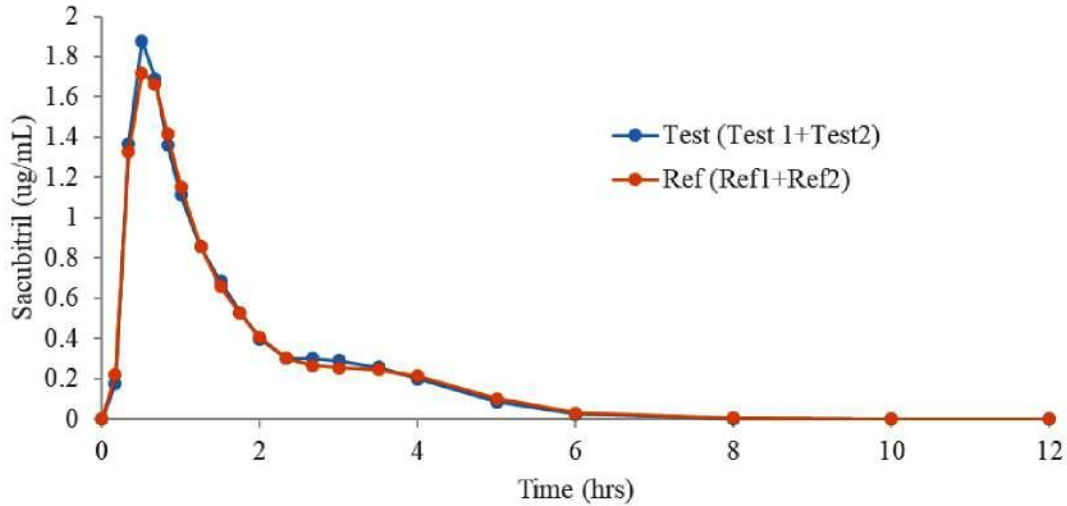
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Valsartan					
Time (hr)	Test (n= 56)		Reference (n= 56)		T/R Ratio
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
0	0	-	0	-	-
0.167	0.17	69.1	0.13	70.59	1.31
0.333	0.83	48.93	0.69	43.83	1.20
0.5	1.63	44.24	1.49	37.53	1.09
0.667	2.51	41.05	2.33	37.89	1.08
0.833	3.34	40.66	3.1	36.53	1.08
1	3.97	40.04	3.71	37.76	1.07
1.25	4.73	38.98	4.44	37.98	1.07
1.5	4.98	37.68	4.79	36.8	1.04
1.75	5.06	36.12	4.9	35.74	1.03
2	4.98	35.63	4.82	35.77	1.03
2.333	4.65	37.51	4.65	34.16	1.00
2.667	4.5	35.95	4.37	33.69	1.03
3	4.25	36.04	4.18	32.4	1.02
3.5	4.11	36.26	3.97	31.35	1.04
4	3.9	36.65	3.81	33.43	1.02
5	3.05	40.35	3.06	36.45	1.00
6	2.09	42.03	2.11	38.47	0.99
8	1.35	42.77	1.38	40.58	0.98
10	0.91	43.9	0.93	41.74	0.98
12	0.64	45.7	0.66	43.16	0.97
16	0.35	51.02	0.35	45.18	1.00
24	0.16	66.49	0.15	56.54	1.07
36	0.07	84.98	0.06	72.4	1.17
48	0.02	172.83	0.02	168.52	1.00

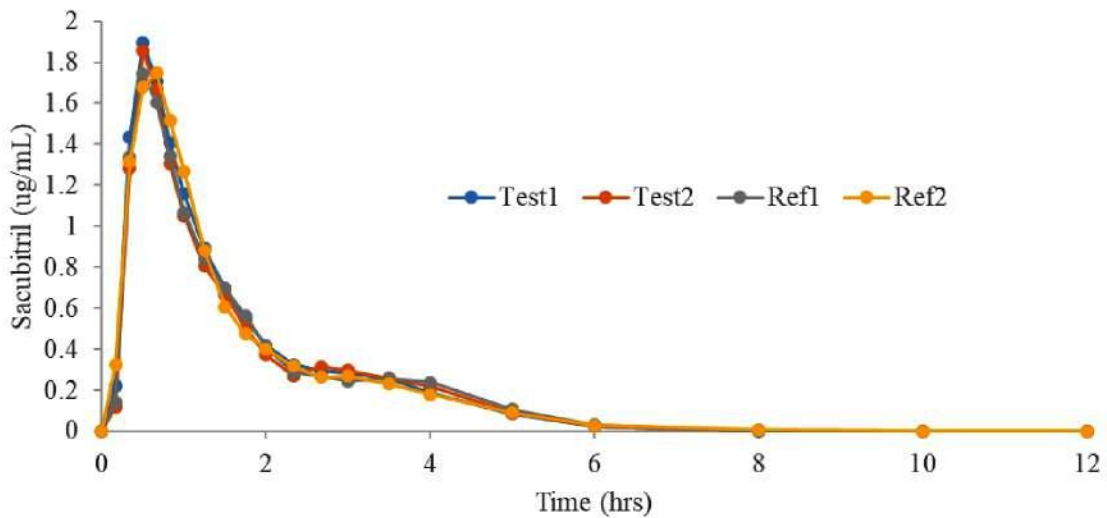
Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study – Assessor’s Results

Sacubitril

Plasma Sacubitril Levels
Sacubitril/Valsartan Tablets, ANDA 213719
Under Fasting Conditions
Dose = 1 x 97 mg/103 mg

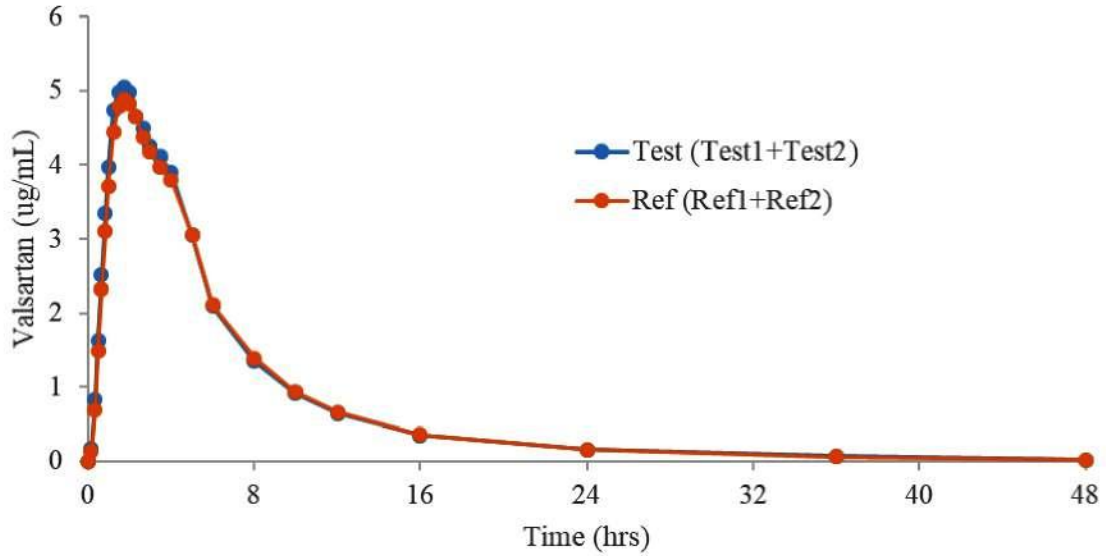


Plasma Sacubitril Levels
Sacubitril/Valsartan Tablets, ANDA 213719
Under Fasting Conditions
Dose = 1 x 97 mg/103 mg

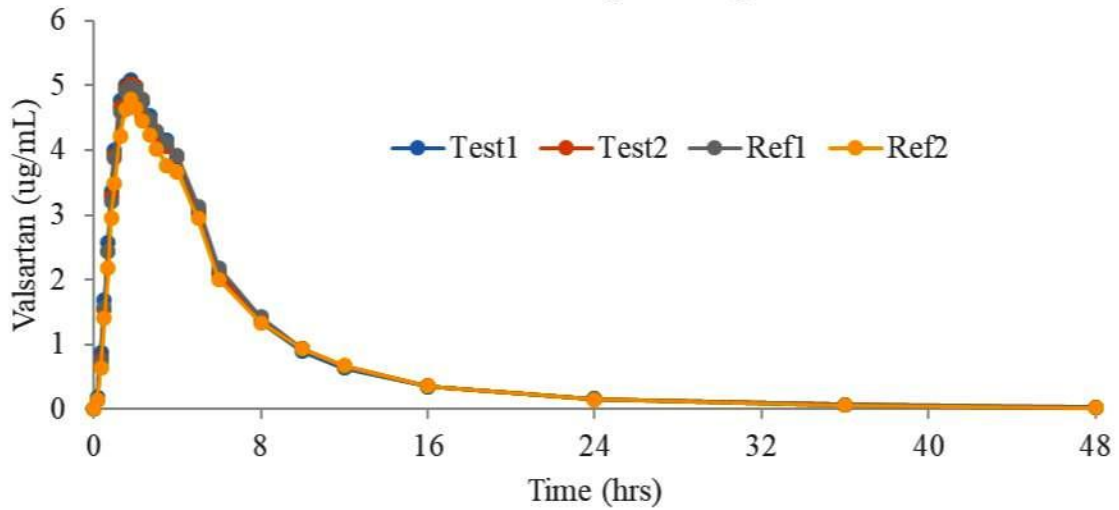


Valsartan

Plasma Valsartan Levels
Sacubitril/Valsartan Tablets, ANDA 213719
Under Fasting Conditions
Dose = 1 x 97 mg/103 mg



Plasma Valsartan Levels
Sacubitril/Valsartan Tablets, ANDA 213719
Under Fasting Conditions
Dose = 1 x 97 mg/103 mg



4.2 Formulation Data

(b)(4)

4.2.1 Updated Test Formulation Table in the 2/24/2020 Submission

Sr. No.	Name of Ingredient	Quantity per Unit (mg)				% w/w**		Function
		24 mg/26 mg	49 mg/51 mg	97 mg/103 mg	24 mg/26 mg	49 mg/51 mg	97 mg/103 mg	
	Sacubitril/Valsartan* ^{(b)(4)}	(b)(4)						Active ingredient
	Microcrystalline Cellulose NF ^{(b)(4)}	(b)(4)						
	Low Substituted Hydroxy Propyl Cellulose NF ^{(b)(4)}	(b)(4)						
	Colloidal Silicon Dioxide, NF ^{(b)(4)}	(b)(4)						
	Sodium Stearyl Fumarate NF	(b)(4)						
	Crospovidone ^{(b)(4)} NF	(b)(4)						
Total (Core Tablet)		102.400	204.800	390.000	-	-	-	
		(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)

Amount of Film Coating Ingredients in Each Strength

(b)(4)

(b)(4)

Iron Oxide Yellow
Iron Oxide Red

(b)(4)

(b)(4)

FD&C Yellow #5/ Tartrazine
Aluminum Lake

FD&C red #40/
aluminum lake

FD&C Blue #2/

(b)(4)

(b)(4)

4.2.2 Inactive Ingredients (IIG Table)

Strength	Excipient	Amount (mg)/ Tablet	Amount (mg)/Day	FDA's IIG Limit (mg, Route of Administration) ¹²	IIG Limit Reference	MDI in Test Formulation Below or Exceeding FDA's IIG Limit
(b)(4)	Microcrystalline Cellulose	(b)(4)				
	Low Substituted Hydroxy	(b)(4)				
	Colloidal Silicon Dioxide					
	Sodium Stearyl Fumarate					
	Crospovidone	(b)(4)				
	Hypromellose	(b)(4)				
			(b)(4)			

¹² IIG-MDD_Master Spreadsheet: <http://sharepoint.fda.gov/orgs/CDER-OGD/BIO/IIGMDD%20Master%20Spreadsheet/Forms/AllItems.aspx?InitialTabId=Ribbon%2EDocument&VisibilityContext=WSSTabPersistence>

¹³ The most recent annual report for the RLD product [GS Review: NDA 207620, New/Annual Report, 8/30/2019 (Module 1.13.5)Summary of manufacturing changes) did not mention formulation changes. The next available annual report [GS Review: NDA 207620, New/Annual Report, 8/30/2018 (Module 1.13.5)Summary of manufacturing changes, p. 15 and 18 of 18)] provided a link to the current RLD formulation, which is GS Review: NDA 207620, New/Annual Report, 8/30/2018 (Module 3.2.P.1)Description and Composition). Therefore, the RLD formulation is from p. 4-6 of 7 of the aforementioned Module 3.2.P.1 document.

(b)(4)	(b)(4)
(b)(4)	Iron Oxide Yellow
	Iron Oxide Red
	Ferrosferric Oxide / (b)(4)
	FD&C Yellow #5/ Tartrazine Aluminum Lake

(b)(4)

(b)(4)

FD&C Red #40/ 344
344 Aluminum
Lake
FD&C Blue #2 344
(b)(4)

(b)(4)

(b)(4)

(b)(4)

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(b) (4)

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

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: Acceptable

- Since the applicant updated the formulation table, the assessor re-evaluated the IIG limits as well as formulation proportionality.
- As with the original formulation table, the updated test formulation also contains

(b)(4)

original BE assessment³ for details) is still current.

(b)(4)

- As with the original formulation table, the updated test formulation also contains FD&C Yellow #5/tartrazine *aluminum lake* for the 97 mg; 103 mg strength. It is noted that FD&C Yellow #5/tartrazine is listed in the internal IIG-MDD database for “general concerns”. The assessor verified that the general concern evaluation for FD&C Yellow #5/tartrazine *aluminum lake* in the original BE assessment (please see Section 4.2 in the original BE assessment³ for details) is still current.

- As with the original formulation table, amount of excipients containing elemental iron in the updated test formulation remains unchanged.

(b)(4)

- The updated formulations for the 24 mg/26 mg and 49 mg/51 mg strengths are proportionally similar to the updated formulation for the 97 mg/103 mg bio-strength of the test product.

4.3 Dissolution Testing

4.3.1 Dissolution Data

4.3.1.1 Dissolution Data – 24 mg/26 mg Strength

4.3.1.1.1 Dissolution Data - Sacubitril/Valsartan Tablets, 24 mg/26 mg [Reference product (Lot: FX000303)] vs. Test product (Batch No.: ME80340)] – Sacubitril

Dissolution Conditions		USP I (Basket)								
Speed of Rotation:		75 RPM								
Medium:		pH 6.8 Phosphate Buffer								
Volume:		900 mL								
Temperature:		37°C ±0.5°C								
Firm's Proposed Specifications		Not less than ☐ % (Q) of the labeled amount of Sacubitril is dissolved in 30 minutes.								
Dissolution Testing Site (Name, Address)		(b)(4)								
Study Ref No.	Testing Date	Product ID\Batch No. (Reference - Exp. Dt.) (Test - Mfg Dt.)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes)				Study Report Location	
Study Report	February 20, 2020	Entresto™ Sacubitril/valsartan tablets, 24 mg/26 mg Batch Number: FX000303 Expiry date: Feb, 2021 Distributed by: Novartis pharmaceuticals corp, East Hanover, NJ07936	24 mg/26 mg, Tablets	12	10	15	20	30	45	
					73.4	94.5	94.8	94.9		94.9
					(b)(4)					2.0
Study Report	February 17, 2020	Sacubitril/Valsartan Tablets, 24mg/26mg Batch Number: ME80340 Mfg. date: Dec. 2018 Mfg. Bv:	24 mg/26 mg, Tablets	12	10	15	20	30	2.1	
					63.8	90.3	99.9	99.9		99.9
					(b)(4)					2.1
					Mean	73.4	94.5	94.8	94.9	94.9
					Range	(b)(4)				
					%CV	2.3	1.7	1.9	1.9	2.0
					Mean	63.8	90.3	99.9	99.9	99.9
					Range	(b)(4)				
					%CV	5.9	2.7	2.1	2.1	2.1
						(b)(4)				

4.3.1.1.2 Dissolution Data - Sacubitril/Valsartan Tablets, 24 mg/26 mg [Reference product (Lot: FX000303)] vs. Test product (Batch No.: ME80340)] - Valsartan

Dissolution Conditions		Apparatus:		USP I (Basket)					
Speed of Rotation:		75 RPM							
Medium:		pH 6.8 Phosphate Buffer							
Volume:		900 mL							
Temperature:		37°C ±0.5°C							
Firm's Proposed Specifications		Not less than ☐ % (Q) of the labeled amount of Valsartan is dissolved in 30 minutes.							
Dissolution Testing Site (Name, Address)		(b)(4)							
Study Ref No.	Testing Date	Product ID\Batch No. (Reference - Exp. Dt.) (Test - Mfg Dt.)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes)	Study Report Location			
Study Report	February 20, 2020	Entresto™ Sacubitril/valsartan tablets, 24 mg/26 mg Batch Number: FX000303 Expiry date: Feb, 2021 Distributed by: Novartis pharmaceuticals corp, East Hanover, NJ07936	24 mg/26 mg, Tablets	12	10	Please refer Module 2.7.1.2			
					15		30		
					74.1	94.7	94.9	95.0	95.1
Study Report	February 17, 2020	Sacubitril/Valsartan Tablets, 24mg/26mg Batch Number: ME80340 Mfg. date: Dec, 2018 Mfg.	24 mg/26 mg, Tablets	12	(b)(4)				
					2.2		1.7	2.0	1.9
					63.1	89.1	98.5	98.5	98.6
		(b)(4)			(b)(4)				
					5.7	2.1			
					2.7	2.1			
					2.1	2.1			
					2.1	2.1			

4.3.1.1.3 Dissolution Data - Sacubitril/Valsartan Tablets, 24 mg/26 mg [Reference product (Lot: FX000303)] vs. Test product (Batch No.: ME80341)] - Sacubitril

Dissolution Conditions		Apparatus: USP I (Basket)							
Speed of Rotation:		75 RPM							
Medium:		pH 6.8 Phosphate Buffer							
Volume:		900 mL							
Temperature:		37°C ±0.5°C							
Firm's Proposed Specifications		Not less than % (Q) of the labeled amount of Sacubitril is dissolved in 30 minutes.							
Dissolution Testing Site (Name, Address)		(b)(4)							
Study Ref No.	Testing Date	Product ID\Batch No. (Reference - Exp. Dt.) (Test - Mfg Dt.)	Dosage Strength & Form	No. of Dosage Units	Mean	Range	%CV	Collection Times (minutes)	Study Report Location
Study Report	February 20, 2020	Entresto™ Sacubitril/valsartan tablets, 24 mg/26 mg Batch Number: FX000303 Expiry date: Feb, 2021 Distributed by: Novartis pharmaceuticals corp, East Hanover, NJ07936	24 mg/26 mg, Tablets	12	73.4	(b)(4)	(b)(4)	10 15 20 30 45	Please refer Module 2.7.1.2
					94.5	94.8	94.9	94.9	
Study Report	February 17, 2020	Sacubitril/Valsartan Tablets, 24mg/26mg Batch Number: ME80341 Mfg. date: Dec. 2018 Mfg.	24 mg/26 mg, Tablets	12	2.3	1.7	1.9	1.9	2.0
					73.8	94.9	99.9	99.9	100.0
					9.3	3.7	1.1	1.2	1.2

4.3.1.1.4 Dissolution Data - Sacubitril/Valsartan Tablets, 24 mg/26 mg [Reference product (Lot: FX000303)] vs. Test product (Batch No.: ME80341)] - Valsartan

Dissolution Conditions		Apparatus: USP I (Basket)							
Speed of Rotation:		75 RPM							
Medium:		pH 6.8 Phosphate Buffer							
Volume:		900 mL							
Temperature:		37°C ±0.5°C							
Firm's Proposed Specifications		Not less than % (Q) of the labeled amount of Valsartan is dissolved in 30 minutes.							
Dissolution Testing Site (Name, Address)		(b)(4)							
Study Ref No.	Testing Date	Product ID\Batch No. (Reference - Exp. Dt.) (Test - Mfg Dt.)	Dosage Strength & Form	No. of Dosage Units	Mean	Range	%CV	Collection Times (minutes)	Study Report Location
Study Report	February 20, 2020	Entresto™ Sacubitril/valsartan tablets, 24 mg/26 mg Batch Number: FX000303 Expiry date: Feb, 2021 Distributed by: Novartis pharmaceuticals corp, East Hanover, NJ07936	24 mg/26 mg, Tablets	12	74.1	(b)(4)	(b)(4)	10 15 20 30 45	Please refer Module 2.7.1.2
					94.7	94.9	95.0	95.1	
Study Report	February 17, 2020	Sacubitril/Valsartan Tablets, 24mg/26mg Batch Number: ME80341 Mfg. date: Dec, 2018 Mfg. (b)(4)	24 mg/26 mg, Tablets	12	2.2	(b)(4)	(b)(4)	1.7 2.0 1.9 2.0	
					72.8	93.3	98.1	98.2	
					9.2	3.7	1.1	1.3	
					9.2	3.7	1.1	1.3	

4.3.1.1.5 Dissolution Data - Sacubitril/Valsartan Tablets, 24 mg/26 mg [Reference product (Lot: FX000303)] vs. Test product (Batch No.: ME80342)] - Sacubitril

Dissolution Conditions		Apparatus: USP I (Basket)					
Speed of Rotation:		75 RPM					
Medium:		pH 6.8 Phosphate Buffer					
Volume:		900 mL					
Temperature:		37°C ±0.5°C					
Firm's Proposed Specifications		Not less than: ☐ % (Q) of the labeled amount of Sacubitril is dissolved in 30 minutes.					
Dissolution Testing Site (Name, Address)		(b)(4)					
Study Ref No.	Testing Date	Product ID\Batch No. (Reference - Exp. Dt.) (Test - Mfg Dt.)	Dosage Strength & Form	No. of Dosage Units	Mean	Collection Times (minutes)	Study Report Location
Study Report	February 20, 2020	Entresto™ Sacubitril/valsartan tablets, 24 mg/26 mg Batch Number: FX000303 Expiry date: Feb, 2021 Distributed by: Novartis pharmaceuticals corp, East Hanover, NJ07936	24 mg/26 mg, Tablets	12	73.4	10 15 20 30 45	Please refer Module 2.7.1.2
					(b)(4)	94.5 94.8 94.9	
Study Report	February 17, 2020	Sacubitril/Valsartan Tablets, 24mg/26mg Batch Number: ME80342 Mfg. date: Dec, 2018 Mfg. (b)(4)	24 mg/26 mg, Tablets	12	2.3	1.7 1.9 1.9 2.0	
					58.3	86.1 98.9 99.9 99.6	
					10.5	5.0 1.9 2.5 1.9 2.0	

4.3.1.1.6 Dissolution Data - Sacubitril/Valsartan Tablets, 24 mg/26 mg [Reference product (Lot: FX000303)] vs. Test product (Batch No.: ME80342)] - Valsartan

Dissolution Conditions		Apparatus: USP I (Basket)										
Speed of Rotation:		75 RPM										
Medium:		pH 6.8 Phosphate Buffer										
Volume:		900 mL										
Temperature:		37°C ±0.5°C										
Firm's Proposed Specifications		Not less than % (Q) of the labeled amount of Valsartan is dissolved in 30 minutes.										
Dissolution Testing Site (Name, Address)		(b)(4)										
Study Ref No.	Testing Date	Product ID\Batch No. (Reference - Exp. Dt.) (Test - Mfg Dt.)	Dosage Strength & Form	No. of Dosage Units	Mean	10	15	20	30	45	Study Report Location	
Study Report	February 20, 2020	Entresto™ Sacubitril/valsartan tablets, 24 mg/26 mg Batch Number: FX000303 Expiry date: Feb, 2021 Distributed by: Novartis pharmaceuticals corp, East Hanover, NJ07936	24 mg/26 mg, Tablets	12	74.1	74.1	94.7	94.9	95.0	95.1	Please refer Module 2.7.1.2	
					Range	(b)(4)						
					%CV	2.2	1.7	2.0	1.9	2.0		
					Mean	57.5	84.7	97.1	98.1	97.7		
Study Report	February 17, 2020	Sacubitril/Valsartan Tablets, 24mg/26mg Batch Number: ME80342 Mfg. date: Dec, 2018 Mfg.	24 mg/26 mg, Tablets	12	Range	(b)(4)						
					%CV	10.3	4.9	2.4	1.9	2.1		

4.3.1.2 Dissolution Data – 49 mg/51 mg Strength

4.3.1.2.1 Dissolution Data - Sacubitril/Valsartan Tablets, 49 mg/51 mg [Reference product (Lot: FX000729)] vs. Test product (Batch No.: ME80343)] - Sacubitril

Dissolution Conditions		Apparatus:		USP I (Basket)							
		Speed of Rotation:		75 RPM							
		Medium:		pH 6.8 Phosphate Buffer							
		Volume:		900 mL							
		Temperature:		37°C ±0.5°C							
Firm's Proposed Specifications		Not less than % (Q) of the labeled amount of Sacubitril is dissolved in 30 minutes.									
Dissolution Testing Site (Name, Address)		(b)(4)									
Study Ref No.	Testing Date	Product ID\Batch No. (Reference - Exp. Dt.) (Test - Mfg Dt.)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes)				Study Report Location		
					10	15	20	30		45	
Study Report	February 15, 2020	Entresto™ Sacubitril/valsartan tablets, 49 mg/51 mg Batch Number: FX000729 Expiry date: Apr, 2022 Distributed by: Novartis pharmaceuticals corp, East Hanover, NJ07936	49 mg/51 mg, Tablets	12	Mean	59.1	82.4	96.2	97.7	97.8	Please refer Module 2.7.1.2
					Range	(b)(4)					
					%CV	4.8	3.4	1.8	1.4	1.1	
Study Report	February 12, 2020	Sacubitril/Valsartan Tablets, 49 mg/51 mg Batch Number: ME80343 Mfg. date: Dec, 2018 Mfg. (b)(4)	49 mg/51 mg, Tablets	12	Mean	47.0	73.4	91.5	98.0	98.4	
					Range	(b)(4)					
					%CV	11.8	6.9	4.2	2.8	2.8	

4.3.1.2.2 Dissolution Data - Sacubitril/Valsartan Tablets, 49 mg/51 mg [Reference product (Lot: FX000729)] vs. Test product (Batch No.: ME80343)] - Valsartan

Dissolution Conditions		Apparatus:		USP I (Basket)		
Speed of Rotation:		75 RPM				
Medium:		pH 6.8 Phosphate Buffer				
Volume:		900 mL				
Temperature:		37°C ±0.5°C				
Firm's Proposed Specifications		Not less than % (Q) of the labeled amount of Valsartan is dissolved in 30 minutes.				
Dissolution Testing Site (Name, Address)		(b)(4)				
Study Ref No.	Testing Date	Product ID\Batch No. (Reference - Exp. Dt.) (Test - Mfg Dt.)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes)	Study Report Location
Study Report	February 15, 2020	Entresto™ Sacubitril/valsartan tablets, 49 mg/51 mg Batch Number: FX000729 Expiry date: Apr, 2022 Distributed by: Novartis pharmaceuticals corp, East Hanover, NJ07936	49 mg/51 mg, Tablets	12	10	Please refer Module 2.7.1.2
					15	
					20	
					30	
					45	
					58.6	
					81.6	
					95.1	
					96.5	
					96.6	
					(b)(4)	
					4.7	
					3.4	
					1.8	
					1.4	
					1.1	
					46.2	
					72.3	
					90.1	
					96.5	
					96.9	
					(b)(4)	
					10.8	
					6.9	
					4.2	
					2.9	
					2.8	

4.3.1.2.3 Dissolution Data - Sacubitril/Valsartan Tablets, 49 mg/51 mg [Reference product (Lot: FX000729)] vs. Test product (Batch No.: ME80344)] - Sacubitril

Dissolution Conditions		Apparatus:		USP I (Basket)							
		Speed of Rotation:		75 RPM							
		Medium:		pH 6.8 Phosphate Buffer							
		Volume:		900 mL							
		Temperature:		37°C ±0.5°C							
Firm's Proposed Specifications		Not less than % (Q) of the labeled amount of Sacubitril is dissolved in 30 minutes.									
Dissolution Testing Site (Name, Address)		(b)(4) 1,									
Study Ref No.	Testing Date	Product ID\Batch No. (Reference - Exp. Dt.) (Test - Mfg Dt.)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes)				Study Report Location		
					10	15	20	30		45	
Study Report	February 15, 2020	Entresto™ Sacubitril/valsartan tablets, 49 mg/51 mg Batch Number: FX000729 Expiry date: Apr, 2022 Distributed by: Novartis pharmaceuticals corp, East Hanover, NJ07936	49 mg/51 mg, Tablets	12	Mean	59.1	82.4	96.2	97.7	97.8	Please refer Module 2.7.1.2
					Range	(b)(4)					
					%CV	4.8	3.4	1.8	1.4	1.1	
Study Report	February 12, 2020	Sacubitril/Valsartan Tablets, 49 mg/51 mg Batch Number: ME80344 Mfg. date: Dec, 2018 Mfg.	49 mg/51 mg, Tablets	12	Mean	45.7	71.8	90.6	99.5	99.4	
					Range	(b)(4)					
					%CV	10.5	7.3	4.1	1.4	1.4	

4.3.1.2.4 Dissolution Data - Sacubitril/Valsartan Tablets, 49 mg/51 mg [Reference product (Lot: FX000729)] vs. Test product (Batch No.: ME80344)] - Valsartan

Dissolution Conditions		Apparatus: USP I (Basket)								
Speed of Rotation:		75 RPM								
Medium:		pH 6.8 Phosphate Buffer								
Volume:		900 mL								
Temperature:		37°C ±0.5°C								
Firm's Proposed Specifications										
Not less than % (Q) of the labeled amount of Valsartan is dissolved in 30 minutes.										
Dissolution Testing Site (Name, Address)										
(b)(4)										
Study Ref No.	Testing Date	Product ID\Batch No. (Reference - Exp. Dt.) (Test - Mfg Dt.)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes)				Study Report Location	
Study Report	February 15, 2020	Entresto™ Sacubitril/valsartan tablets, 49 mg/51 mg Batch Number: FX000729 Expiry date: Apr, 2022 Distributed by: Novartis pharmaceuticals corp, East Hanover, NJ07936	49 mg/51 mg, Tablets	12	10	15	20	30	45	Please refer Module 2.7.1.2
					58.6	81.6	95.1	96.5	96.6	
					(b)(4)					
					Mean					
					Range					
					%CV	4.7	3.4	1.8	1.4	1.1
Study Report	February 12, 2020	Sacubitril/Valsartan Tablets, 49 mg/51 mg Batch Number: ME80344 Mfg. date: Dec, 2018 Mfg.	49 mg/51 mg, Tablets	12	10	15	20	30	45	
					45.5	71.1	89.6	98.3	98.3	
					(b)(4)					
					Mean					
					Range					
					%CV	10.1	7.3	4.1	1.4	1.5

4.3.1.2.5 Dissolution Data - Sacubitril/Valsartan Tablets, 49 mg/51 mg [Reference product (Lot: FX000729)] vs. Test product (Batch No.: ME80345)] - Sacubitril

Dissolution Conditions		Apparatus:		USP I (Basket)								
		Speed of Rotation:		75 RPM								
		Medium:		pH 6.8 Phosphate Buffer								
		Volume:		900 mL								
		Temperature:		37°C ±0.5°C								
Firm's Proposed Specifications		Not less than % (Q) of the labeled amount of Sacubitril is dissolved in 30 minutes.										
Dissolution Testing Site (Name, Address)		(b)(4)										
Study Ref No.	Testing Date	Product ID\Batch No. (Reference - Exp. Dt.) (Test - Mfg Dt.)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes)				Study Report Location			
					10	15	20	30		45		
Study Report	February 15, 2020	Entresto™ Sacubitril/valsartan tablets, 49 mg/51 mg Batch Number: FX000729 Expiry date: Apr, 2022 Distributed by: Novartis pharmaceuticals corp, East Hanover, NJ07936	49 mg/51 mg, Tablets	12	Mean	59.1	82.4	96.2	97.7	97.8	Please refer Module 2.7.1.2	
					Range	(b)(4)						
					%CV	4.8	3.4	1.8	1.4	1.1		
Study Report	February 15, 2020	Sacubitril/Valsartan Tablets, 49 mg/51 mg Batch Number: ME80345 Mfg. date: Dec, 2018 Mfg. (b)(4)	49 mg/51 mg, Tablets	12	Mean	44.9	72.2	90.3	98.1	98.1		
					Range	(b)(4)						
					%CV	8.7	4.4	2.0	1.5	1.5		

4.3.1.2.6 Dissolution Data - Sacubitril/Valsartan Tablets, 49 mg/51 mg [Reference product (Lot: FX000018)] vs. Test product (Batch No.: ME80345)] - Valsartan

Dissolution Conditions		Apparatus:		USP I (Basket)		
Speed of Rotation:		75 RPM				
Medium:		pH 6.8 Phosphate Buffer				
Volume:		900 mL				
Temperature:		37°C ±0.5°C				
Firm's Proposed Specifications		Not less than % (Q) of the labeled amount of Valsartan is dissolved in 30 minutes.				
Dissolution Testing Site (Name, Address)		(b)(4)				
Study Ref No.	Testing Date	Product ID\Batch No. (Reference - Exp. Dt.) (Test - Mfg Dt.)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes)	Study Report Location
Study Report	February 15, 2020	Entresto™ Sacubitril/valsartan tablets, 49 mg/51 mg Batch Number: FX000729 Expiry date: Apr, 2022 Distributed by: Novartis pharmaceuticals corp, East Hanover, NJ07936	49 mg/51 mg, Tablets	12	10	Please refer Module 2.7.1.2
					15	
					20	
					30	
					45	
					58.6	
					81.6	
					95.1	
					96.5	
					96.6	
					(b)(4)	
					4.7	
					3.4	
					1.8	
					1.4	
					1.1	
					44.6	
					71.3	
					89.2	
					96.9	
					(b)(4)	
					8.4	
					4.4	
					2.0	
					1.5	
					1.5	

4.3.1.3 Dissolution Data – 97 mg/103 mg Strength

4.3.1.3.1 Dissolution Data - Sacubitril/Valsartan Tablets, 97 mg/103 mg [Reference product (Lot: FX000024)] vs. Test product (Batch No.: ME80346) - **Sacubitril**

Dissolution Conditions		Apparatus: USP I (Basket)									
Speed of Rotation:		75 RPM									
Medium:		pH 6.8 Phosphate Buffer									
Volume:		900 mL									
Temperature:		37°C ±0.5°C									
Firm's Proposed Specifications		Not less than % (Q) of the labeled amount of Sacubitril is dissolved in 30 minutes.									
Dissolution Testing Site (Name, Address)		(b)(4)									
Study Ref No.	Testing Date	Product ID\Batch No. (Reference - Exp. Dt.) (Test - Mfg Dt.)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes)			Study Report Location			
Study Report	February 20, 2020	Entresto™ Sacubitril/valsartan tablets, 97 mg/103 mg Batch Number: FX000024 Expiry date: May, 2020 Distributed by: Novartis pharmaceuticals corp, East Hanover, NJ07936	97 mg/103 mg, Tablets	12	10	15	20	30	45		
					Mean	53.4	78.0	91.4	98.4	98.5	Please refer Module 2.7.1.2
Study Report	February 20, 2020	Sacubitril/Valsartan Tablets, 97 mg/103 mg Batch Number: ME80346 Mfg. date: Dec, 2018 Mfg. 	97 mg/103 mg, Tablets	12	Range	(b)(4)					
					%CV	5.5	4.2	2.6	1.1	1.1	
					Mean	39.6	64.0	82.5	97.0	97.4	
					Range	(b)(4)					
					%CV	17.7	11.9	7.2	1.6	1.2	

4.3.1.3.2 Dissolution Data - Sacubitril/Valsartan Tablets, 97 mg/103 mg [Reference product (Lot: FX000024)] vs. Test product (Batch No.: ME80346)] - Valsartan

Dissolution Conditions		Apparatus:		USP I (Basket)		
Speed of Rotation:		75 RPM				
Medium:		pH 6.8 Phosphate Buffer				
Volume:		900 mL				
Temperature:		37°C ±0.5°C				
Firm's Proposed Specifications		Not less than % (Q) of the labeled amount of Valsartan is dissolved in 30 minutes.				
Dissolution Testing Site (Name, Address)		(b)(4)				
Study Ref No.	Testing Date	Product ID\Batch No. (Reference - Exp. Dt.) (Test - Mfg Dt.)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes)	Study Report Location
Study Report	February 20, 2020	Entresto™ Sacubitril/valsartan tablets, 97 mg/103 mg Batch Number: FX000024 Expiry date: May, 2020 Distributed by: Novartis pharmaceuticals corp, East Hanover, NJ07936	97 mg/103 mg, Tablets	12	10	Please refer Module 2.7.1.2
					15	
					52.7	96.9
					76.8	96.9
					Mean	
					Range	
					(b)(4)	
					%CV	
					5.5	1.1
					4.1	1.0
					2.6	
					81.1	
					Mean	
					39.1	95.7
					63.0	
					Range	
					(b)(4)	
					%CV	
					17.5	1.2
					11.8	1.6
					7.2	
					1.6	

4.3.1.3.3 Dissolution Data - Sacubitril/Valsartan Tablets, 97 mg/103 mg [Reference product (Lot: FX000024)] vs. Test product (Batch No.: ME80347)] - Sacubitril

Dissolution Conditions		Apparatus:		USP I (Basket)							
Speed of Rotation:		75 RPM									
Medium:		pH 6.8 Phosphate Buffer									
Volume:		900 mL									
Temperature:		37°C ±0.5°C									
Firm's Proposed Specifications		Not less than % (Q) of the labeled amount of Sacubitril is dissolved in 30 minutes.									
Dissolution Testing Site (Name, Address)		(b)(4)									
Study Ref No.	Testing Date	Product ID\Batch No. (Reference - Exp. Dt.) (Test - Mfg Dt.)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes)				Study Report Location		
					10	15	20	30		45	
Study Report	February 20, 2020	Entresto™ Sacubitril/valsartan tablets, 97 mg/103 mg Batch Number: FX000024 Expiry date: May, 2020 Distributed by: Novartis pharmaceuticals corp, East Hanover, NJ07936	97 mg/103 mg, Tablets	12	Mean	53.4	78.0	91.4	98.4	98.5	Please refer Module 2.7.1.2
					Range	(b)(4)					
					%CV	5.5	4.2	2.6	1.1	1.1	
Study Report	February 11, 2020	Sacubitril/Valsartan Tablets, 97 mg/103 mg Batch Number: ME80347 Mfg. date: Dec, 2018 Mfg. (b)(4)	97 mg/103 mg, Tablets	12	Mean	28.3	53.1	72.5	95.5	98.2	
					Range	(b)(4)					
					%CV	15.4	9.3	7.2	2.9	1.0	

4.3.1.3.4 Dissolution Data – Sacubitril/Valsartan Tablets, 97 mg/103 mg [Reference product (Lot: FX000024)] vs. Test product (Batch No.: ME80347)] - Valsartan

Dissolution Conditions		Apparatus:		USP I (Basket)						
Speed of Rotation:		75 RPM								
Medium:		pH 6.8 Phosphate Buffer								
Volume:		900 mL								
Temperature:		37°C ±0.5°C								
Firm's Proposed Specifications		Not less than % (Q) of the labeled amount of Valsartan is dissolved in 30 minutes.								
Dissolution Testing Site (Name, Address)		(b)(4)								
Study Ref No.	Testing Date	Product ID\Batch No. (Reference - Exp. Dt.) (Test - Mfg Dt.)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes)				Study Report Location	
					10	15	20	30		45
Study Report	February 20, 2020	Entresto™ Sacubitril/valsartan tablets, 97 mg/103 mg Batch Number: FX000024 Expiry date: May, 2020 Distributed by: Novartis pharmaceuticals corp, East Hanover, NJ07936	97 mg/103 mg, Tablets	12	Mean	52.7	76.8	90.0	96.9	Please refer Module 2.7.1.2
					Range	(b)(4)				
					%CV	5.5	4.1	2.6	1.0	
Study Report	February 11, 2020	Sacubitril/Valsartan Tablets, 97 mg/103 mg Batch Number: ME80347 Mfg. date: Dec, 2018 Mfg. (b)(4)	97 mg/103 mg, Tablets	12	Mean	28.6	52.9	72.0	94.8	97.3
					Range	(b)(4)				
					%CV	14.4	9.2	7.2	2.9	

4.3.1.3.5 Dissolution Data – Sacubitril/Valsartan Tablets, 97 mg/103 mg [Reference product (Lot: FX000024)] vs. Test product (Batch No.: ME80348) - Sacubitril

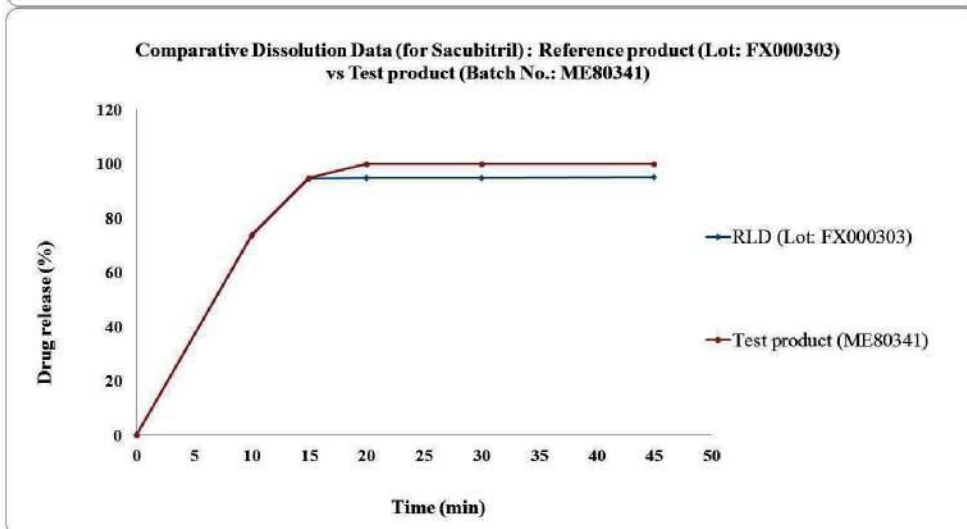
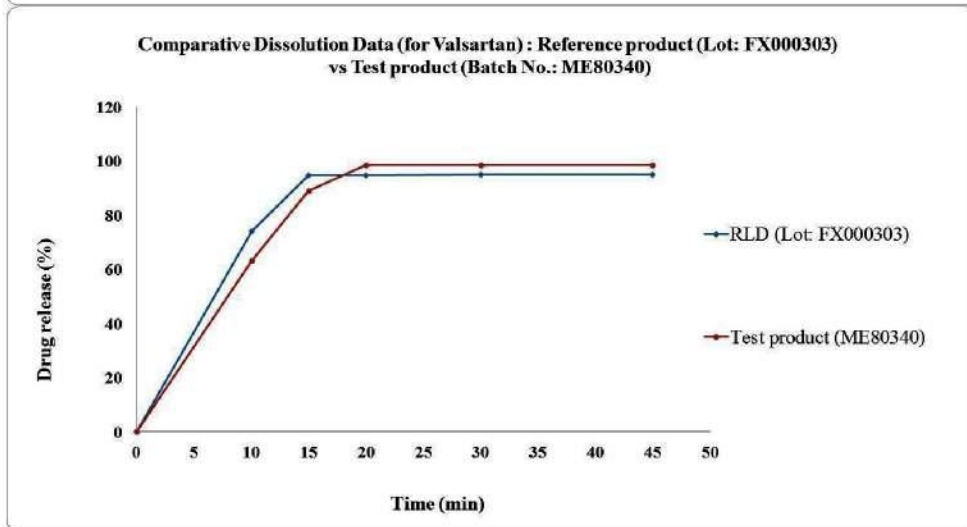
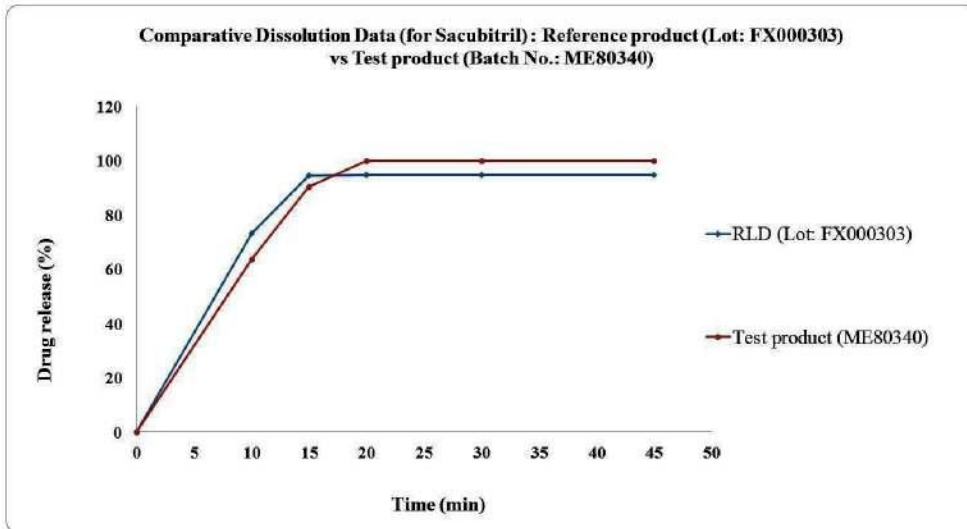
Dissolution Conditions		Apparatus:		USP I (Basket)							
Speed of Rotation:		75 RPM									
Medium:		pH 6.8 Phosphate Buffer									
Volume:		900 mL									
Temperature:		37°C ±0.5°C									
Firm's Proposed Specifications		Not less than % (Q) of the labeled amount of Sacubitril is dissolved in 30 minutes.									
Dissolution Testing Site (Name, Address)		(b)(4)									
Study Ref No.	Testing Date	Product ID\Batch No. (Reference - Exp. Dt.) (Test - Mfg Dt.)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes)			Study Report Location			
					10	15	20		30	45	
Study Report	February 20, 2020	Entresto™ Sacubitril/valsartan tablets, 97 mg/103 mg Batch Number: FX000024 Expiry date: May, 2020 Distributed by: Novartis pharmaceuticals corp, East Hanover, NJ07936	97 mg/103 mg, Tablets	12	Mean	53.4	78.0	91.4	98.4	98.5	Please refer Module 2.7.1.2
					Range	(b)(4)					
					%CV	5.5	4.2	2.6	1.1	1.1	
Study Report	February 12, 2020	Sacubitril/Valsartan Tablets, 97 mg/103 mg Batch Number: ME80348 Mfg. date: Dec, 2018 Mfg. (b)(4)	97 mg/103 mg, Tablets	12	Mean	26.1	52.8	73.6	96.9	98.9	
					Range	(b)(4)					
					%CV	18.3	9.5	6.4	2.0	1.0	

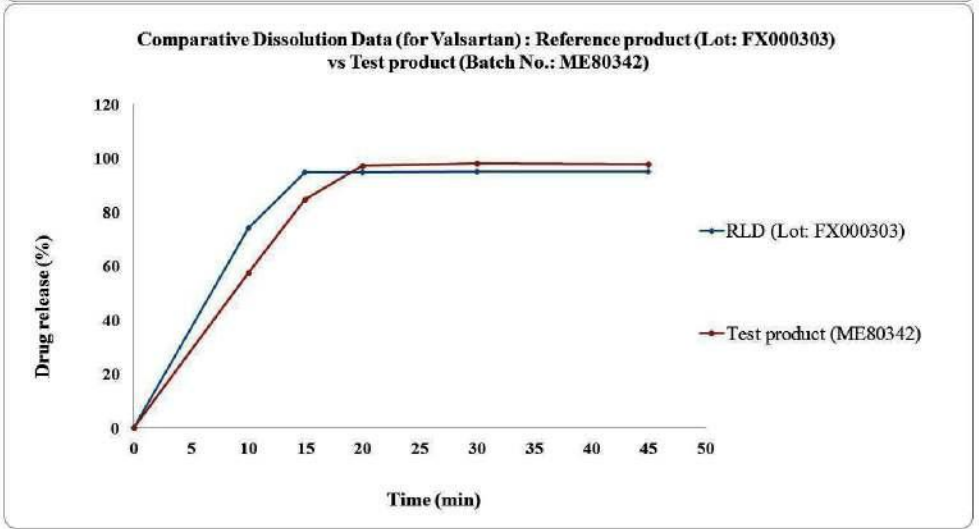
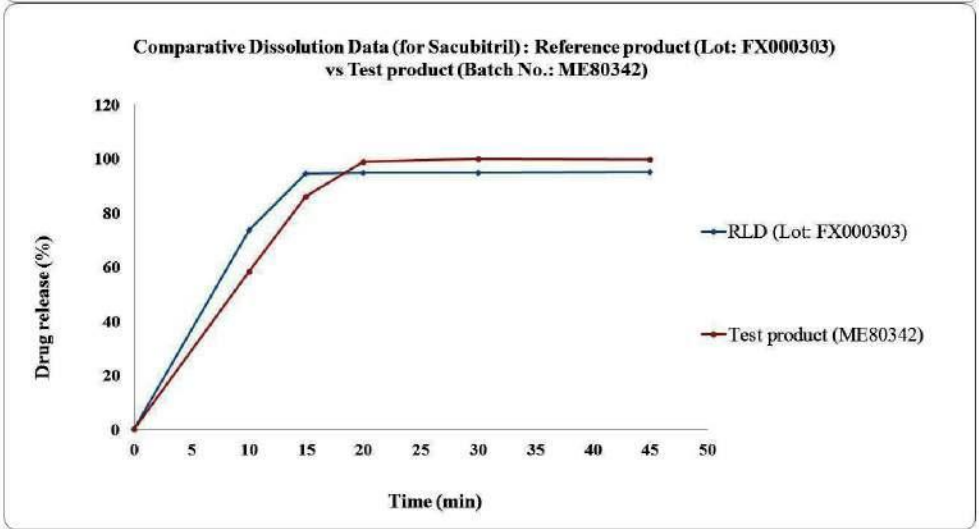
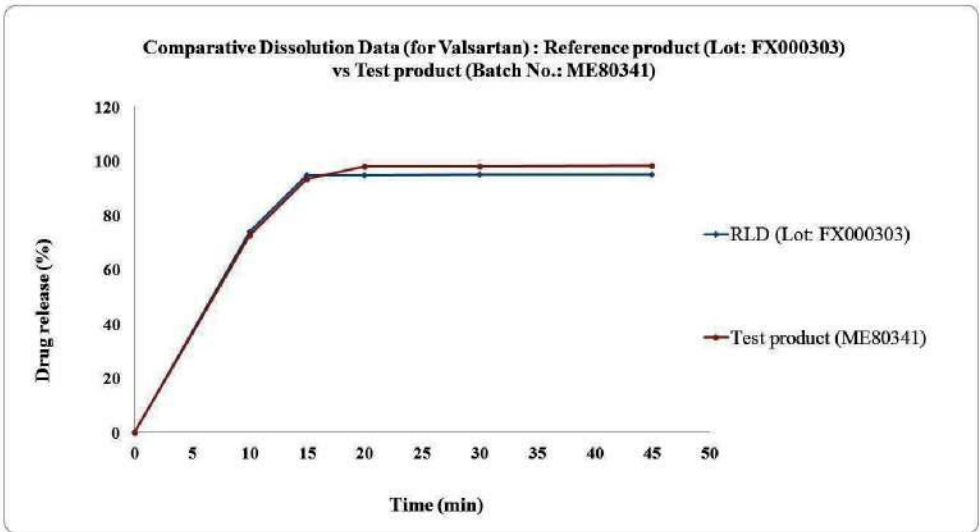
4.3.1.3.6 Dissolution Data – Sacubitril/Valsartan Tablets, 97 mg/103 mg [Reference product (Lot: FX000024)] vs. Test product (Batch No.: ME80348)] - Valsartan

Dissolution Conditions		Apparatus:		USP I (Basket)		
Speed of Rotation:				75 RPM		
Medium:				pH 6.8 Phosphate Buffer		
Volume:				900 mL		
Temperature:				37°C ±0.5°C		
Firm's Proposed Specifications		Not less than % (Q) of the labeled amount of Valsartan is dissolved in 30 minutes.				
Dissolution Testing Site (Name, Address)				(b)(4)		
Study Ref No.	Testing Date	Product ID\Batch No. (Reference - Exp. Dt.) (Test - Mfg Dt.)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes)	Study Report Location
Study Report	February 20, 2020	Entresto™ Sacubitril/valsartan tablets, 97 mg/103 mg Batch Number: FX000024 Expiry date: May, 2020 Distributed by: Novartis pharmaceuticals corp, East Hanover, NJ07936	97 mg/103 mg, Tablets	12	10	Please refer Module 2.7.1.2
					15	
					20	
					30	
					45	
					52.7	
					76.8	
					90.0	
					96.9	
					96.9	
					Mean	
					Range	
					%CV	
					5.5	
					4.1	
					2.6	
					1.0	
					1.1	
					Mean	
					26.3	
					52.4	
					72.9	
					96.0	
					97.9	
					Range	
					(b)(4)	
					%CV	
					17.0	
					9.5	
					6.4	
					1.9	
					1.0	

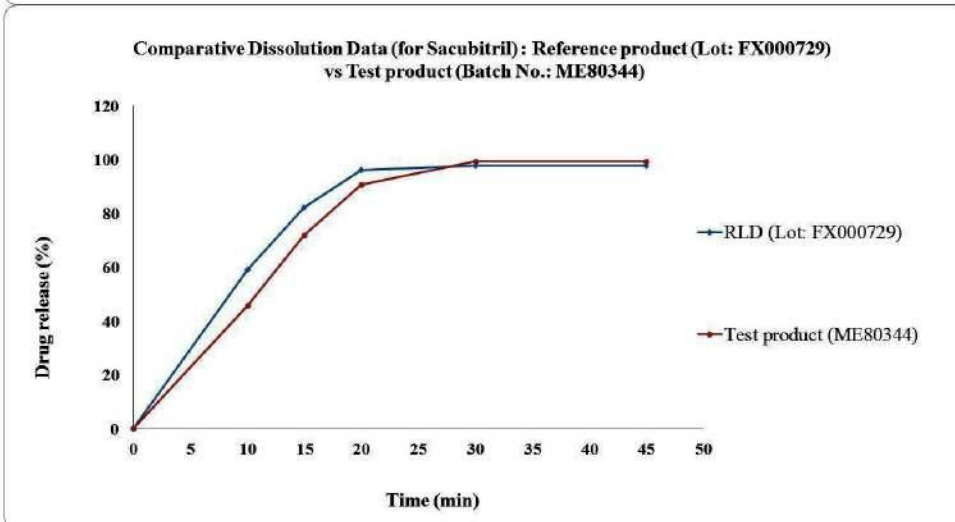
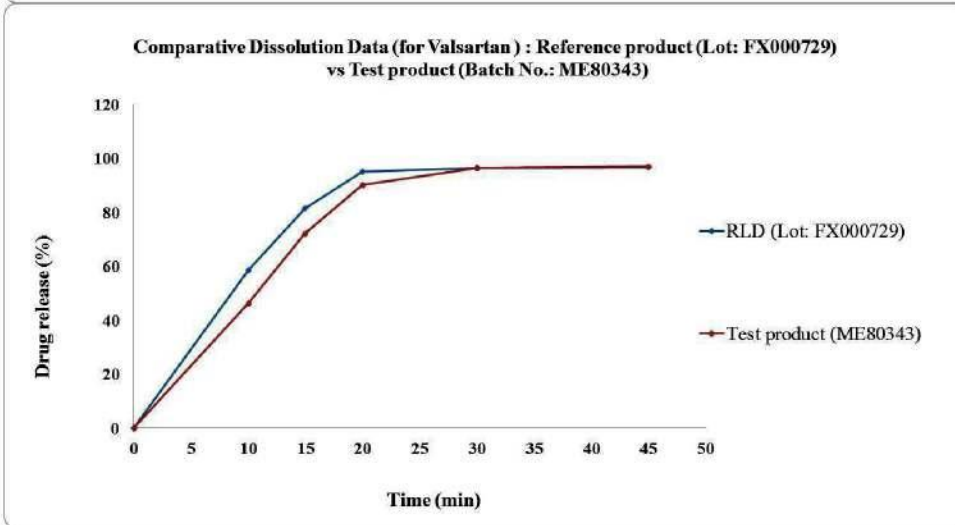
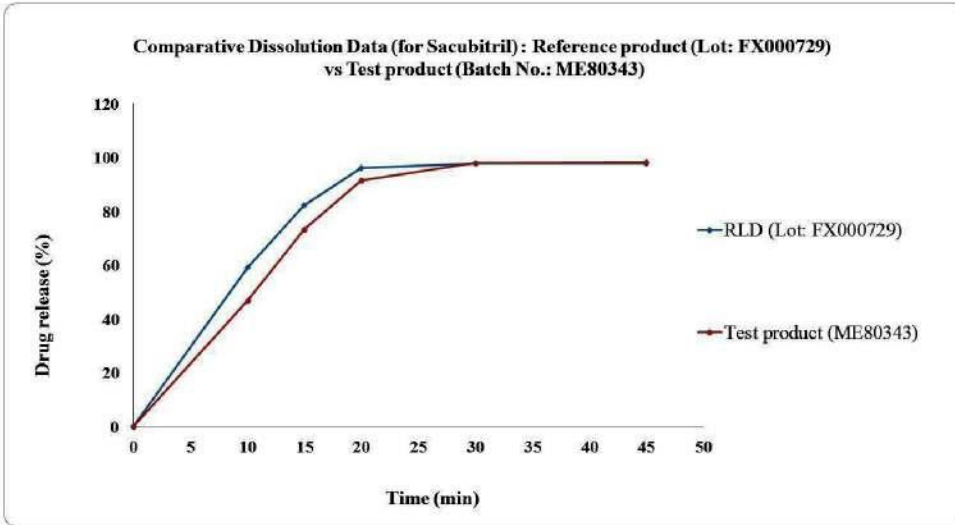
4.3.2 Dissolution Profiles

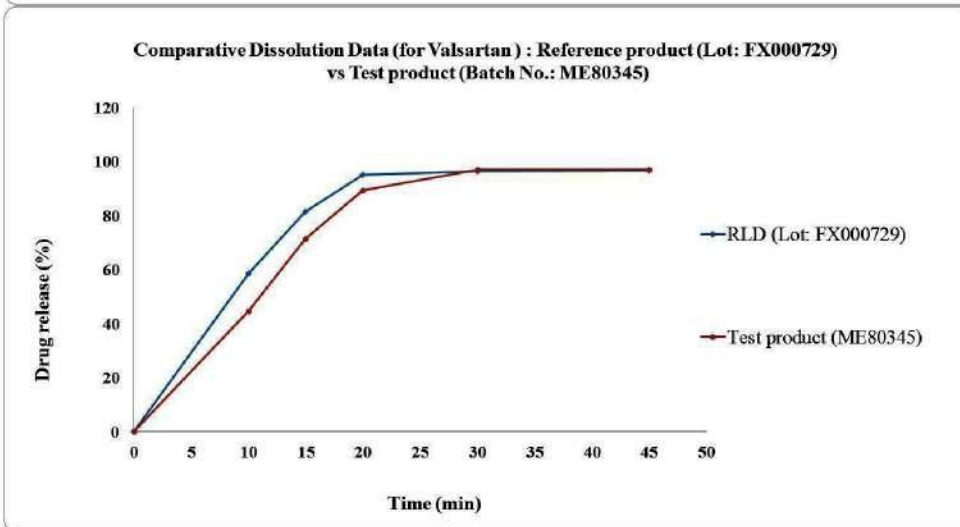
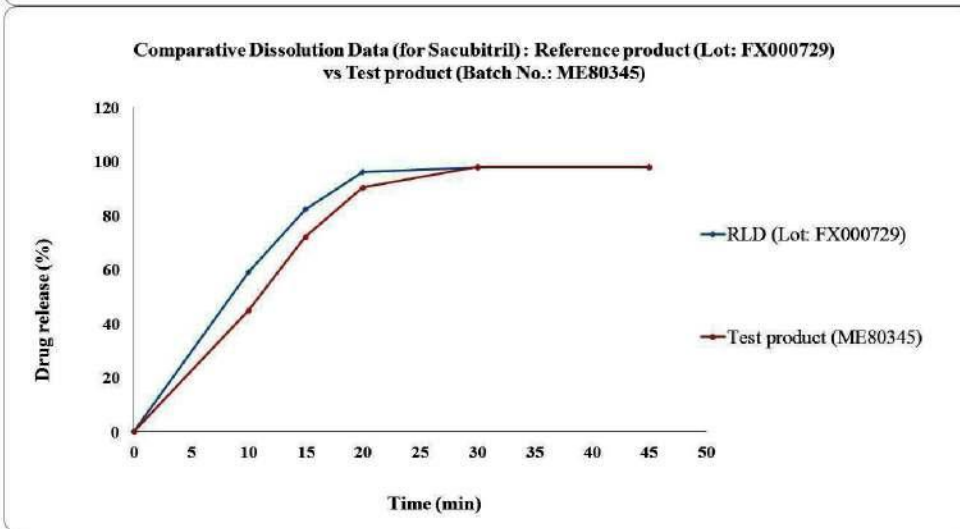
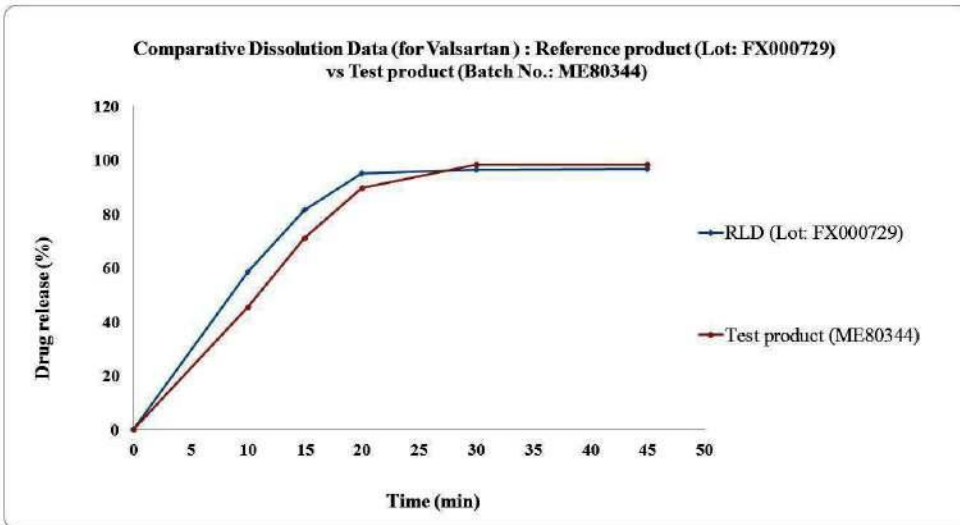
4.3.2.1 Dissolution Profiles – 24 mg/26 mg Strength



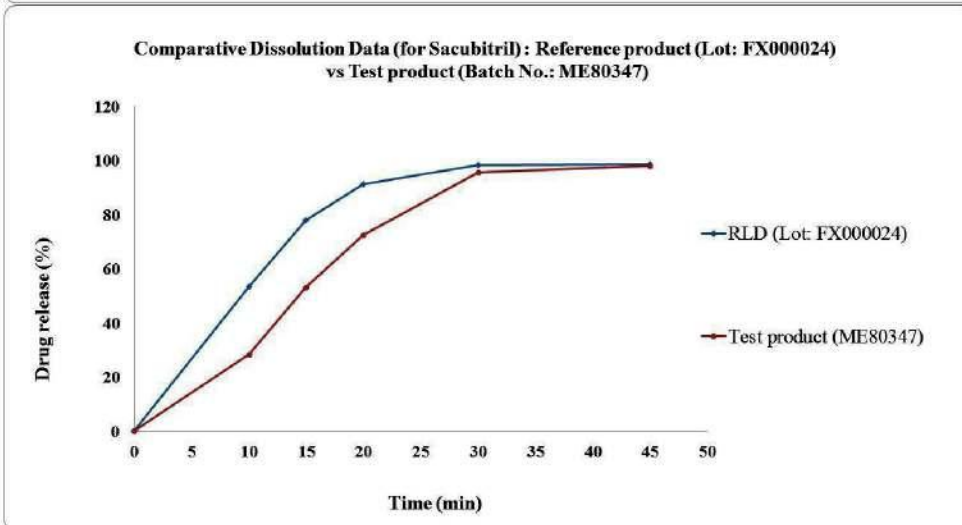
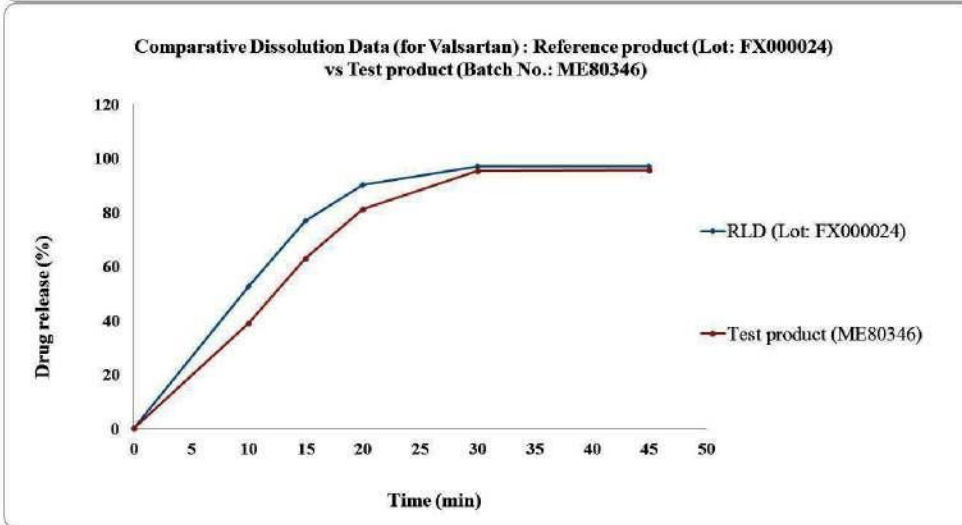
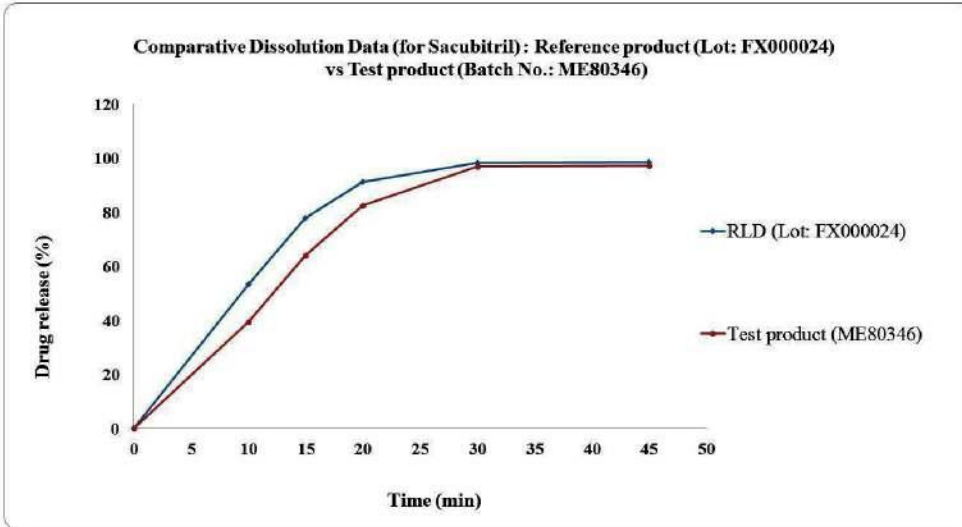


4.3.2.2 Dissolution Profiles – 49 mg/51 mg Strength

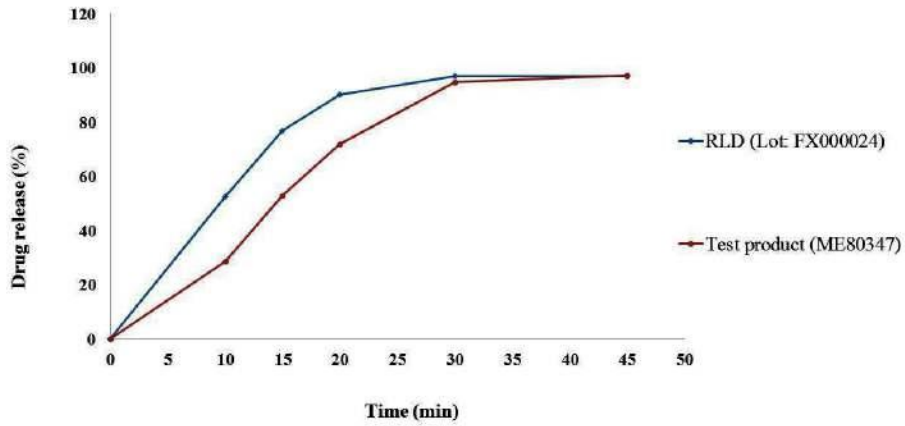




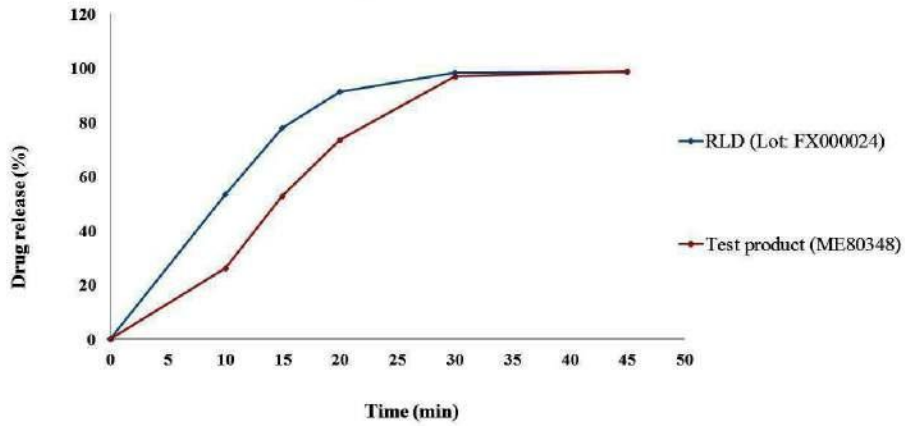
4.3.2.3 Dissolution Profiles – 97 mg/103 mg Strength



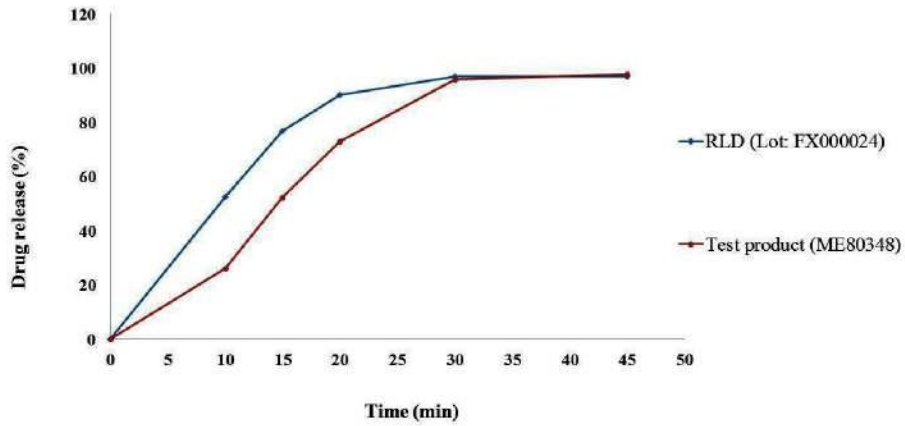
Comparative Dissolution Data (for Valsartan) : Reference product (Lot: FX000024)
vs Test product (Batch No.: ME80347)



Comparative Dissolution Data (for Sacubitril) : Reference product (Lot: FX000024)
vs Test product (Batch No.: ME80348)



Comparative Dissolution Data (for Valsartan) : Reference product (Lot: FX000024)
vs Test product (Batch No.: ME80348)



4.3.3 F2 Metric

F2 metric calculated?	☐ Yes ☒ No
If no, reason why F2 not calculated	(b)(4)
Please comment on whether dissolution data are adequate to support requests submitted under 21 CFR 320.22(d)(2) or 320.24(b)(6).	Adequate

Overall Comments: Acceptable

- The applicant re-conducted the comparative *in vitro* dissolution study for 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg strengths between the test and reference products using the current FDA-recommended dissolution method (900 mL of pH 6.8 phosphate buffer using USP Apparatus I at 75 rpm). This new dissolution method is considered acceptable by biopharmaceutics assessor.¹⁰
- For each of the 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg strengths, the QC dissolution test was conducted on 1 unexpired reference batch and 3 test batches. For the 97 mg/103 mg strength, the reference batch (batch #FX000024) and 1 of the 3 test batches (test batch #ME80346) were the same batches used in the fasting and fed studies. For the 24 mg/26 mg strength, the reference batch (batch #FX000303) and 1 of the 3 test batches (test batch #ME80340) were the same batches used in the non-pivotal fasting study.
- It is noted that the applicant did not provide certificate of analysis for the reference batch #FX000729 of the 49 mg/51 mg strength (this is a different reference batch as compared to the one used in the original dissolution study for the 49 mg/51 mg strength). Since this is a dissolution study for biowaiver purposes, and another study report²⁰ also mentioned that the expiration date of this batch is Apr, 2022, which is consistent with the date listed in the dissolution summary tables, the assessor will not pursue this issue further.
- Based on the mean dissolution data, both the test and reference products showed rapid dissolution profiles (- % drug release within 30 minutes).

The dissolution data are **acceptable** to support biowaiver for the 24 mg/26 mg and 49 mg/51 mg strengths of the test product.

²⁰ GS Review: ANDA 213719, Quality/Response to Discipline Review Letter, 2/24/2020 (Module 3.2.P.2\Suspension Study Report, p. 4 of 19).

4.4 Attachments

4.4.1 SAS Output

Study	Analyte	Purpose	SAS Data	SAS Code	SAS Stat	SAS Output/Table
Fasting (97 mg/103 mg strength)	Sacubitril	PK analysis	 213719_Fasting_Dat asets_Sacubitril.doc	 TWOWAYCALCKE fasting SAC 12hr for	 213719_Fasting_sta t_SacubitrilACTUAL.c	 213719_Fasting_tab le_SacubitrilACTUAL.
		Statistical analysis	 SAC firm reorg reviewer KE 12hr an	 HV-RefScale4Period -ver1 A213719 fastin	 213719-STAT OUTPUT.doc	 213719-ANALYSIS.d oc
	Valsartan	PK analysis	 213719_Fasting_Dat asets_Valsartan.doc	 TWOWAYCALCKE fasting VAL for PK c	 213719_Fasting_sta t_ValsartanACTUAL.c	 213719_Fasting_tab le_ValsartanACTUAL.
		Statistical analysis	 VAL firm reorg reviewer KE and PK.>	 HV-RefScale4Period -ver1 A213719 fastin	 213719-STAT OUTPUT.doc	 213719-ANALYSIS.d oc

NOTE TO DBI PROJECT MANAGER and REGULATORY PROJECT MANAGER (RPM): As per OGD Policy, two Citizen Petitions (CPs) are pending for this drug product which state the following:

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

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

Citizen petition (FDA-2019-P-2869) for Multiple drug products containing valsartan, which requests FDA to: 1) review and significantly lower the acceptable intake/permitted daily exposure limit of DMF, as listed in the current FDA guidance Q3C – Tables and List, Guidance for Industry, from its current level of 8,800,000 nanograms to less than 1,000 nanograms (and potentially as low as 96 nanograms); 2) request a recall of identified lots of valsartan on the basis that, due to contamination with a probable human carcinogen, these drugs are adulterated under Section 501 of the FDCA (21 U.S.C. § 351) and misbranded under Section 502 of the FDCA (21 U.S.C. § 352); 3) conduct examinations and investigation under Section 702 (a) of the FDCA (21 U.S.C. § 372(a)) regarding these products, their manufacturing processes, and the manufacturer submissions made for FDA approval under 704 (a) of the FDCA (21 U.S.C. § 374(a)) and effect labeling revisions as needed.

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

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 213719
APPLICANT: Zydus Pharmaceuticals (USA) Inc.
DRUG PRODUCT: Sacubitril/Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg

The Division of Bioequivalence I (DBI) has completed its review and has no further questions at this time.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if chemistry, manufacturing and controls, microbiology, labeling, or other scientific, regulatory or inspectional issues or concerns arise in the future. Please be advised that these concerns may result in the need

for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Utpal Munshi, Ph.D.
Acting Director, Division of Bioequivalence I
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

4.5 Outcome Page

Completed Assignment for 213719 ID: 41817

Reviewer: Ma, Tian

Date

Completed:

Verifier: ,

Date Verified:

Division: Division of Bioequivalence

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

Items:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Score</i>	<i>Subtotal</i>		
41817	1/9/2020	BIO	ANDA Amendment [1]	1	1	Edit	Delete
41817	1/9/2020	Parallel	Minor Amendment (Original or Supplement) [1]	1	1	Edit	Delete
				Total:	2		

DIVISION OF BIOEQUIVALENCE ASSESSMENT

ANDA No.	213719		
Drug Product Name	Sacubitril/Valsartan Tablets		
Strength(s)	24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg		
Applicant Name	Zydus Pharmaceuticals (USA) Inc.		
Applicant Address	73-B, Route 31 North Pennington, NJ 08534		
US Contact Name and US Mailing Address	Srinivas Gurrum (Srini), VP & Head of RA & QA - North America/ Dhaval N. Desai- Manager, Reg. Affairs 73-B, Route 31 North Pennington, NJ 08534 grrinivas@zydususa.com		
US Contact Telephone Number	(b)(6)		
US Contact Fax Number	609-730-1999		
Original Submission Date(s)	7/8/2019		
Submission Date(s) of Amendment(s) Under Assessment	N/A		
Primary Assessor	Tian Ma, Ph.D.		
Secondary Assessor	Amanda Jones, Ph.D.		
Tertiary Assessor	N/A		
Study Number(s)	BA18086532	BA17861024-01	BA18086667
Study Type(s)	Fasting	Fed	Fasting (additional)
Strength(s)	97 mg/103 mg	97 mg/103 mg	24 mg/26 mg
Clinical Site	Cliantha Research Limited		
Clinical Site Address	1st floor, Silver Arcade, Near Ashwamegh III, Samrajya, Mujmahuda Road, Akota, Vadodara-390020, Gujarat, India		
Analytical Site	(b)(4)		
Analytical Site Address			
Study Number(s)	BA17861001-01	BA17861002-01	
Study Type(s)	Fasting (pilot)	Fed (pilot)	
Strength(s)	97 mg/103 mg	97 mg/103 mg	

Clinical Site	Cliantha Research Limited		
Clinical Site Address	1 st floor, Silver Arcade, Near Ashwamegh III, Samrajya, Mujmahuda Road, Akota, Vadodara-390020, Gujarat, India		
Analytical Site	(b)(4)		
Analytical Site Address			
Office of Study Integrity and Surveillance (OSIS) status	<u>Backlog, Year 1 and Year 2 ANDAs</u> ☐ Pending ☐ Complete ☐ 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 ☒ 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	N/A		
Justification for Major Designation	N/A		
Overall Assessment Result	☐ Adequate ☒ Inadequate		
Product Specific Guidance (PSG) Referenced in Assessment	☒ Recommended/Latest Revision Date: <u>April 2016</u> <u>RLD Number: 207620</u> ☐ 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	Fasting	97 mg/ 103 mg	☐ Adequate ☒ Inadequate
1	Fed	97 mg/ 103 mg	☐ Adequate ☒ Inadequate

¹ Requests submitted under 21 CFR 320.22(d)(2) or 320.24(b)(6).

1	Waiver/Deem Bioequivalent	24 mg/26 mg ² and 49 mg/51 mg	☐ Adequate ☒ Inadequate

1 EXECUTIVE SUMMARY

This application contains the results of fasting and fed bioequivalence (BE) studies comparing a test product Zydus Pharmaceuticals (USA) Inc.'s Sacubitril/Valsartan Tablets, 97 mg/103 mg to the corresponding reference product Novartis Pharmaceuticals Corp's Entresto® (sacubitril/valsartan) Tablets, 97 mg/103 mg. The fasting BE study was designed as a single-dose, two-treatment, two-sequence, four-period, fully replicated study in healthy male subjects, and the fed BE study was designed as a single-dose, two-way crossover study in healthy male subjects. The applicant's fasting and fed BE studies are **incomplete** due to bioanalytical deficiencies (for both fasting and fed study) and incomplete dataset (for fasting study only). The applicant's results for the fasting study and the assessor's results for the fed study are summarized in the tables below. The assessor will verify the applicant's results upon receipt of the applicant's response to the attached deficiency letter.

Fasting Study BA18086532 – Applicant's Results

Sacubitril and Valsartan Tablets, 97 mg/ 103 mg 1 x 97 mg/ 103 mg Fasting Bioequivalence Study No. BA18086532, N=34 (Male=34 and Female=0) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Sacubitril					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (hr *µg/ml)	2.491	2.523	0.9872	95.78	101.75
AUC _∞ (hr *µg/ml)	2.521	2.551	0.9882	95.88	101.85
C _{max} (µg/ml)	1.850	1.898	0.9745	NA	NA
Valsartan					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (hr *µg/ml)	31.441	31.454	0.9996	NA	NA
AUC _∞ (hr *µg/ml)	31.951	31.960	0.9997	NA	NA
C _{max} (µg/ml)	5.099	4.930	1.0343	NA	NA

² In the current submission, the applicant submitted a pivotal fasting pharmacokinetic (PK) for the 24 mg/26 mg strength. However, given all 3 strengths of the test product is rapidly dissolving based on the mean dissolution data, there is a potential that this rapidly dissolving observation could be used to support biowaiver of the lower 2 strengths, if the applicant could adequately address the biopharmaceutics assessor's concern on the dissolution method [currently, the biopharmaceutics assessor considers the applicant's dissolution method inadequate (GDRP: ANDA-213719-ORIG-1, Biopharmaceutics Review, A213719 Biopharm R01.IQ.docx, 12/11/2019)]. Therefore, this fasting study for the 24 mg/26 mg strength is not extensively assessed in the current assessment. In the future, if the applicant could not resolve the dissolution method issue, then this fasting study may be assessed extensively.

Fasting Bioequivalence Study No. BA18086532								
Sacubitril								
Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	Outcome
LAUCt	NA	95.78%	101.75%	0.0078	0.088	NA	Average Bioequivalence	Bioequivalent
LAUCi	NA	95.88%	101.85%	0.0077	0.088	NA	Average Bioequivalence	Bioequivalent
LCmax	0.97	NA	NA	0.1338	0.366	-0.0672	Scaled Average Bioequivalence	Bioequivalent
Valsartan								
Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	Outcome
LAUCt	1.00	NA	NA	0.1056	0.325	-0.0553	Scaled Average Bioequivalence	Bioequivalent
LAUCi	1.00	NA	NA	0.1032	0.321	-0.0541	Scaled Average Bioequivalence	Bioequivalent
LCmax	1.03	NA	NA	0.1291	0.359	-0.0652	Scaled Average Bioequivalence	Bioequivalent

Fed Study BA17861024-01 – Assessor's Results

Sacubitril and Valsartan Tablets, 97 mg/ 103 mg 1 x 97 mg/ 103 mg Fed Bioequivalence Study No. BA17861024-01, N=36 (Male=36 and Female=0) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Sacubitril					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (hr *µg/ml)	2.37	2.42	0.98	95.14	101.27
AUC _∞ (hr *µg/ml)	2.40	2.44	0.98	95.28	101.41
C _{max} (µg/ml)	1.57	1.70	0.92	83.01	102.53
Valsartan					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (hr *µg/ml)	16.53	16.43	1.01	93.86	107.84
AUC _∞ (hr *µg/ml)	16.88	16.82	1.00	93.73	107.46
C _{max} (µg/ml)	2.60	2.58	1.01	93.93	108.10

Additional Studies

The applicant also submitted in vivo data of the following 3 additional studies:

- One passing fasting study for the 24 mg/26 mg strength (Study # BA18086667)
- One pilot fasting study for the 97 mg/103 mg strength (Study #BA17861001-01)
- One pilot fed study for the 97 mg/103 mg strength (Study #BA17861002-01)

The fasting study for the 24 mg/26 mg strength (Study # BA18086667), designed as a single-dose, two-treatment, two-sequence, four-period, fully replicated study in healthy male subjects, and was conducted using the same test and reference batches as compared to the pivotal fasting and fed studies for the 97 mg/103 mg strength. The applicant conducted this study because their f2 value in the dissolution study using the QC dissolution method is less than 50 for 24 mg/26 mg strength in comparison with 97 mg/103 mg strength for both sacubitril and valsartan.³ However, it is noted that the test and reference products showed rapid dissolution profiles based on mean dissolution data, hence no f2 calculation was conducted by the assessor. Since there is a potential that this rapidly dissolving observation could be used to support biowaiver of the 24 mg/26 mg and 49 mg/51 mg strengths, if the applicant could adequately address the biopharmaceutics assessor's concern on the dissolution method (currently, the biopharmaceutics assessor considers the applicant's dissolution method inadequate⁴). Therefore, this fasting study for the 24 mg/26 mg strength is not extensively assessed in the current assessment. In the future, if the applicant could not resolve the dissolution method issue to support biowaiver, then this fasting study may be assessed extensively.

The pilot fasting (Study #BA17861001-01) and fed (Study #BA17861002-01) studies were designed as a single-dose, three-period, three-treatment, three-sequence crossover study in healthy male subjects. These pilot studies used different test batch (#97+103-F031A) but same reference batch as compared to the pivotal fasting and fed studies. The formulation of the test batch used in these pilot studies is the same as that of the bio-batch used in the pivotal fasting and fed studies.

No deaths or serious adverse events (SAEs) were reported during these 3 additional BE studies.

In addition, the applicant also mentioned that additional pilot fasting and fed studies (study # not specified) were conducted using test batch (#97+103-F030A) that does not have the same formulation as compared to the bio-batch.⁵ Therefore, the applicant did not provide summary tables for these pilot studies. The applicant also did not mention whether there

³ GS Review: ANDA 213719, New/ANDA, 7/8/2019 (Module 5.3.1.2. BA 18086532...Study Report Body5.3.1.2. Comparative BA/BE Study Reports and Related Information, p. 9-12 of 14).

⁴ GDRP: ANDA-213719-ORIG-1, Biopharmaceutics Review, A213719 Biopharm R01.IQ.docx, 12/11/2019.

⁵ GS Review: ANDA 213719, New/ANDA, 7/8/2019 (Module 2.7.1\2.7.1 Summary of Biopharmaceutic Studies..., p. 13 of 134).

were any deaths or SAEs reported during these pilot studies using test batch #97+103-F030A. However, given that these pilot studies did not use the same test formulation as compared to the bio-batch as stated by the applicant, and the 2 pivotal studies as well as the 3 other additional studies (study #s BA18086667, BA17861001-01 and BA17861002-01) did not report SAEs or deaths, and only reported limited number of AEs, the risk of SAE and death in these pilot studies using test batch #97+103-F030A is low. Therefore, the assessor will not ask the applicant to specify if any SAEs or deaths were reported for these pilot studies.

In vitro comparative dissolution study

The applicant has conducted dissolution testing on Sacubitril and Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg, using an in-house method (b)(4) (b)(4) that is consistent with the previous FDA-recommended dissolution method, but different from the current FDA-recommended method that was updated on 10/24/2019 [900 mL of pH 6.8 phosphate buffer (degassed) using *USP Apparatus I at 75 rpm*). According to the dissolution-only assessment⁴, the applicant's dissolution method is inadequate. The biopharmaceutics assessor states that the proposed dissolution method "is not acceptable at this stage because (b)(4)

(b)(4) The dissolution testing data for 24 mg/26 mg and 49 mg/51 mg strengths are incomplete to support biowaiver of these 2 strengths due to deficiencies in dissolution method.

At this time, the Division of Bioequivalence I (DBI) **cannot grant** the biowaiver for *in vivo* BE study requirements for 24 mg/26 mg and 49 mg/51 mg strengths based on criteria set forth in 21 CFR § 320.22 (d)(2) due to deficiencies related to the BE studies and in vitro comparative dissolution studies.

Formulation

The formulations of the test product are acceptable for all 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg strengths. The 24 mg/26 mg and 49 mg/51 mg strengths of the test product are proportionally similar to the bio-strength (97 mg/103 mg).

The Office of Study Integrity and Surveillance (OSIS) Status

For the clinical site of the fasting and fed studies, Office of Study Integrity and Surveillance (OSIS) determines that an inspection is not warranted at this time.⁶ For the analytical site of the fasting and fed studies, OSIS inspected the site for other ANDAs (b)(4)

⁶ GDRP: ANDA-213719-ORIG-1, Application Life Cycle, Site: CLIANTHA RESEARCH LIMITED

(b)(4)

(b)(4) Per the inspection report, the inspection at the analytical site is classified as No Action Indicated (NAI), and OSIS states that the data from studies of similar design that were not audited but submitted to pending applications (including the fasting and fed studies of the current ANDA) are reliable for Agency review. In addition, the studies submitted in the current ANDA do not indicate any conduct issues and no data integrity deficiencies were identified by the assessor. The OSIS inspection status of the current ANDA is complete.

The application is **incomplete**.

NOTE TO DBI PROJECT MANAGER and REGULATORY PROJECT MANAGER (RPM): As per OGD Policy, a Citizen Petition (CP) is pending for this drug product which states the following:

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

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

Citizen petition (FDA-2019-P-2869) for Multiple drug products containing valsartan, which requests FDA to: 1) review and significantly lower the acceptable intake/permitted daily exposure limit of DMF, as listed in the current FDA guidance Q3C – Tables and List, Guidance for Industry, from its current level of 8,800,000 nanograms to less than 1,000 nanograms (and potentially as low as 96 nanograms); 2) request a recall of identified lots of valsartan on the basis that, due to contamination with a probable human carcinogen, these drugs are adulterated under Section 501 of the FDCA (21 U.S.C. § 351) and misbranded under Section 502 of the FDCA (21 U.S.C. § 352); 3) conduct examinations and investigation under Section 702 (a) of the FDCA (21 U.S.C. § 372(a)) regarding these products, their manufacturing processes, and the manufacturer submissions made for FDA approval under 704 (a) of the FDCA (21 U.S.C. § 374(a)) and effect labeling revisions as needed.

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

(b)(4)

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3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Drug Product and Strength(s)	Sacubitril/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 Date⁸	Novartis Pharmaceuticals Corp NDA 207620 Approved on 7/7/2015
Reference Listed Drug (RLD) and Strength(s)	Entresto® (sacubitril/valsartan) Tablets, 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg
RLD Holder; NDA/ANDA Number; Approval Date⁸	Please see RS information above

3.2 PK/PD Information⁹

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	- When pregnancy is detected, discontinue ENTRESTO as soon as possible. - Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus.
Bioavailability	The oral absolute bioavailability of sacubitril is estimated to be $\geq 60\%$. The valsartan in ENTRESTO is more bioavailable than the valsartan in other marketed tablet formulations; 26 mg, 51 mg, and

⁸ Electronic Orange Book:

https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=207620

Last accessed: 8/2/2019.

⁹ Drugs@FDA: <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process>

Last accessed: 12/10/2019.

	103 mg of valsartan in ENTRESTO is equivalent to 40 mg, 80 mg, and 160 mg of valsartan in other marketed tablet formulations, respectively.
Food Effect	ENTRESTO administration with food has no clinically significant effect on the systemic exposures of sacubitril, LBQ657, or valsartan. Although there is a decrease in exposure to valsartan when ENTRESTO is administered with food, this decrease is not accompanied by a clinically significant reduction in the therapeutic effect. ENTRESTO can therefore be administered with or without food.
Tmax	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	<u>Adults:</u> Sacubitril / Valsartan – 97/103 mg, twice daily (2 x 97/103 mg = 194 mg / 206 mg). <u>Pediatric:</u> • ≥50 kg: 97/103 mg, twice daily (2 x 97/103 mg = 194 mg / 206 mg). • ≥40 kg to <50 kg: 72 mg/78 mg, twice daily (3 x 24/26 mg x 2 times daily = 144 mg / 156 mg). • < 40 kg: 3.1 mg/kg (combined amount of Sacubitril / Valsartan, twice daily (3.1 * 40 = 124 * 2 = 248 mg combined Sacubitril / Valsartan daily). [3.1 x 40 = 124 x 2 times daily = 248 mg combined Sacubitril / Valsartan daily which is equivalent to 2.5 x 49/51 tablet as used to prepare oral suspension recommended in pediatric patients less than 40 kg = 122.5 mg/127.5 mg Sacubitril / Valsartan daily.] Safety and effectiveness have not been established in pediatric patients less than 1 year of age.

3.3 OGD Recommendations for Drug Product

Source of most recent recommendations or provide the embedded document to the current draft guidance	 guidance.pdf https://www.accessdata.fda.gov/drugsatfda_docs/psg/Sacubitril;%20Valsartan_oral%20tablet_RLD%20207620_RC04-16.pdf	
Summary of OGD or DB History	Approved ANDAs:	No ¹⁰
	Pending ANDAs:	Yes ¹¹ (multiple)
	Controls:	Yes ¹² (none from the current applicant)
	Protocols:	No ¹³
	Pending Citizen Petitions and other legal and regulatory issues: If yes, please comment.	☒ Yes ¹⁴ (please see detail below) ☐ No

Citizen Petition:

According to the most recent OGD Policy Alert List (as of 12/20/2019), currently there is 1 citizen petition [FDA-2019-P-1893, filed on 4/19/2019] that affects sacubitril and valsartan tablets. The petitioner requests the 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. The issues raised by this petition are currently under review by the Agency, and FDA has not made a final decision on these issues. The reviewer's comments in this review reflect FDA's current thinking only.

According to the most recent OGD Policy Alert List (as of 12/20/2019), currently there is 1 citizen petition [FDA-2019-P-2869] that affects Multiple drug products containing valsartan, which requests FDA to: 1) review and significantly lower the acceptable intake/permitted daily exposure limit of DMF, as listed in the current FDA guidance Q3C – Tables and List, Guidance for Industry, from its current level of 8,800,000 nanograms to less than 1,000 nanograms (and potentially as low as 96 nanograms); 2) request a recall of identified lots of valsartan on the basis that, due to contamination with a probable human carcinogen, these drugs are adulterated under Section 501 of the FDCA (21 U.S.C. § 351) and misbranded under Section 502 of the FDCA (21 U.S.C. § 352); 3) conduct examinations and investigation under Section 702 (a) of the FDCA (21 U.S.C. § 372(a))

¹⁰ Electronic Orange Book. Search term: sacubitril. Last accessed: 8/2/2019.

¹¹ DARRTS, Application search. Search term: sacubitril. Last accessed: 8/2/2019.

¹² GDRP: Controls Project Search (search by keywords "entresto"). Last accessed: 8/2/2019.

¹³ GDRP (search by keywords "entresto"). Last accessed: 8/2/2019.

¹⁴ OGD Policy Alert List as of 12/20/2019, <http://sharepoint.fda.gov/orgs/CDER-OGD/OGDP/OGD%20Policy%20Alert/SitePages/Home.aspx>. Last accessed: 12/15/2019.

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.

Per the current OGD Policy Alert, no approval actions can be taken prior to contacting Policy Lead and all disciplines can continue communications (CRL, IR/DRL).

3.4 Pre-Study Bioanalytical Method Validation

Sacubitril

Information Requested	Data	
Bioanalytical method validation report location	7/8/2019 submission, Module 5.3.1.4. BA18086532... \attachment-6-1-method-val-report and \attachment-6-2-addendum-1-method-val-reports, which is the same as Module 5.3.1.4. BA17861024-01... \attachment-6-1-method-val-report and \attachment-6-2-addendum-1-method-val-reports	
Analyte	Sacubitril	
Internal standard (IS)	Sacubitril D4	
Method description	Solid phase extraction with LC/MS/MS method	
Limit of quantitation	0.01000 µg/mL	
Recovery of drug at each QC (%CV)	Avg.: 93.3% (%CV: 1.0%) HQC: 94.2% MQC-1: 92.2% MQC-2: 92.7% LQC: 93.9%	
Average recovery of IS (%)	107%	
Standard curve concentrations (µg/mL)	0.01000, 0.02000, 0.04000, 0.1000, 0.3000, 0.6000, 1.200, 2.400, 4.800 and 6.000 µg/mL	
QC concentrations (µg/mL)	LLOQ QC	0.01000 µg/mL
	LQC	0.03000 µg/mL
	MQC-2	0.3600 µg/mL
	MQC-1	2.100 µg/mL
	HQC	4.500 µg/mL
QC Intraday precision range (%)	LLOQ QC	2.1-3.7%
	LQC	1.0-3.6%
	MQC-2	0.6-1.6%
	MQC-1	1.4-2.4%
	HQC	1.3-2.9%
QC Intraday accuracy range (%)	LLOQ QC	102-112%
	LQC	107-111%
	MQC-2	107-108%
	MQC-1	100-101%
	HQC	93.6-98.6%
QC Interday precision range (%)	LLOQ QC	5.1%
	LQC	2.9%
	MQC-2	1.1%
	MQC-1	2.1%
	HQC	2.9%
QC Interday accuracy range (%)	LLOQ QC	106%
	LQC	109%

	MQC-2	107%									
	MQC-1	101%									
	HQC	96.1%									
Bench-top stability (hrs)	27 hours at room temperature (15°C to 30°C) (For Sacubitril) 27 hours at room temperature (15°C to 30°C) [For Sacubitril fortified with Metabolite Sacubitrilat (LBQ657) and 4-Hydroxy Valsartan (6.000/12.00 µg/mL)]										
Stock stability (days)	34 days at refrigerator temperature (2°C to 10°C)										
Processed stability (hrs)	121 hours at room temperature (15°C to 30°C) and at refrigerator temperature (2°C to 10°C) (For Sacubitril) 124 hours at room temperature (15°C to 30°C) and 123 hours at refrigerator temperature (2°C to 10°C) [For Sacubitril fortified with Metabolite Sacubitrilat (LBQ657) and 4-Hydroxy Valsartan (6.000/ 12.00 µg/mL)]										
Freeze-thaw stability (cycles)	6 cycles (for Sacubitril) 6 cycles [For Sacubitril fortified with Metabolite Sacubitrilat (LBQ657) and 4-Hydroxy Valsartan (6.000/12.00 µg/mL)]										
Long-term storage stability (days)	97 days at -20°C ± 10°C temperature (For Sacubitril) 98 days at -20°C ± 10°C temperature [For Sacubitril fortified with Metabolite Sacubitrilat (LBQ657) and 4-Hydroxy Valsartan (6.000/12.00 µg/mL)]										
Dilution integrity	9.00 µg/mL (1.5 x highest calibration standard), 2-fold dilution, and 48.00 µg/mL (8 x highest calibration standard), 10-fold dilution										
		<table border="1"> <thead> <tr> <th></th> <th>%CV</th> <th>%Bias</th> </tr> </thead> <tbody> <tr> <td>2-fold Dilution</td> <td>1.0</td> <td>-7.4</td> </tr> <tr> <td>10-fold Dilution</td> <td>1.7</td> <td>-3.3</td> </tr> </tbody> </table>		%CV	%Bias	2-fold Dilution	1.0	-7.4	10-fold Dilution	1.7	-3.3
	%CV	%Bias									
2-fold Dilution	1.0	-7.4									
10-fold Dilution	1.7	-3.3									
Selectivity[®]	No significant interfering peak noted in blank plasma lots										

[®] From Method Validation Addendum-I

Valsartan

Information Requested	Data
Bioanalytical method validation report location	7/8/2019 submission, Module 5.3.1.4. BA18086532... \attachment-6-1-method-val-report and \attachment-6-2-addendum-1-method-val-reports, which is the same as Module 5.3.1.4. BA17861024-01... \attachment-6-1-method-val-report and \attachment-6-2-addendum-1-method-val-reports
Analyte	Valsartan
Internal standard (IS)	Valsartan D9
Method description	Solid phase extraction with LC/MS/MS method
Limit of quantitation	0.02000 µg/mL
Recovery of drug at each QC (%CV)	Avg.: 91.1% (%CV: 0.7%) HQC: 92.0% MQC-1: 90.4% MQC-2: 90.9%

	LQC: 91.0%	
Average recovery of IS (%)	95.6%	
Standard curve concentrations (µg/mL)	0.02000, 0.04000, 0.08000, 0.2000, 0.6000, 1.200, 2.400, 4.800, 9.600 and 12.00 µg/mL	
QC concentrations (µg/mL)	LLOQ QC	0.02000 µg/mL
	LQC	0.06000 µg/mL
	MQC-2	0.7200 µg/mL
	MQC-1	4.200 µg/mL
	HQC	9.000 µg/mL
QC Intraday precision range (%)	LLOQ QC	2.7-5.1%
	LQC	2.5-3.5%
	MQC-2	0.9-1.7%
	MQC-1	1.3-1.9%
	HQC	0.9-2.0%
QC Intraday accuracy range (%)	LLOQ QC	99.3-107%
	LQC	103-107%
	MQC-2	103-104%
	MQC-1	97.7-99.6%
	HQC	94.1-98.3%
QC Interday precision range (%)	LLOQ QC	5.2%
	LQC	3.3%
	MQC-2	1.3%
	MQC-1	1.8%
	HQC	2.4%
QC Interday accuracy range (%)	LLOQ QC	103%
	LQC	105%
	MQC-2	103%
	MQC-1	98.4%
	HQC	95.9%
Bench-top stability (hrs)	27 hours at room temperature (15°C to 30°C) (For Valsartan) 27 hours at room temperature (15°C to 30°C) [For Valsartan fortified with Metabolite Sacubitrilat (LBQ657) and 4-Hydroxy Valsartan (6.000/12.00 µg/mL)]	
Stock stability (days)	34 days at refrigerator temperature (2°C to 10°C)	
Processed stability (hrs)	121 hours at room temperature (15°C to 30°C) and at refrigerator temperature (2°C to 10°C) (For Valsartan) 124 hours at room temperature (15°C to 30°C) and 123 hours at refrigerator temperature (2°C to 10°C) [For Valsartan fortified with Metabolite Sacubitrilat (LBQ657) and 4-Hydroxy Valsartan (6.000/ 12.00 µg/mL)]	
Freeze-thaw stability (cycles)	6 cycles (for Valsartan) 6 cycles [For Valsartan fortified with Metabolite Sacubitrilat (LBQ657) and 4-Hydroxy Valsartan (6.000/12.00 µg/mL)]	
Long-term storage stability (days)	97 days at -20°C ± 10°C temperature (For Valsartan) 98 days at -20°C ± 10°C temperature [For Valsartan fortified with Metabolite Sacubitrilat (LBQ657) and 4-Hydroxy Valsartan (6.000/12.00 µg/mL)]	

Dilution integrity	18.00 µg/mL (1.5 x highest calibration standard), 2-fold dilution, and 96.00 µg/mL (8 x highest calibration standard), 10-fold dilution		
		%CV	%Bias
	2-fold Dilution	2.0	-9.5
	10-fold Dilution	1.5	-3.9
Selectivity [@]	No significant interfering peak noted in blank plasma lots		

[@] From Method Validation Addendum-I

SOP for bioanalytical method validation submitted?	☒ Yes ¹⁵ ☐ No
Is the same anticoagulant used in the pre-method validation study and BE sample analysis? If not, was cross validation study conducted?	To be determined (K2EDTA used in method validation as well as fasting and fed studies, but unclear which anticoagulant was used in method validation addendum. <u>The applicant will be asked to specify.</u>)
Does the duration of the each of the LTSS stability parameters support the sample preparation/assay duration and clinical study sample storage temperature?	☒ Yes ☐ No LTSS: 98 days at -20±10°C [For Sacubitril and Valsartan fortified with Metabolite Sacubitrilat (LBQ657) and 4-Hydroxy Valsartan (6.000/12.00 µg/mL)] Fasting: 38 days at -20±10°C Fed: 23 days at -20±10°C
Was the % recovery consistent across QC concentrations?	☒ Yes ☐ No
Was the pre-study validation of the bioanalytical method used for the pivotal bioequivalence studies acceptable?	☐ Yes ☒ No

Comments on the Pre-Study Method Validation: Incomplete

- The applicant conducted method validation addendum to support change in analytical site in the company from the one used in the method validation to the one used in the fasting and fed studies. However, it is unclear what anticoagulant was used in this method validation addendum. Therefore, the applicant will be asked to specify.
- It is noted that the instruments used in the fasting and fed studies (Instruments
(b)(4)) are not validated in the method validation or its addendum. However, it is noted that 1) these instruments are of the same type (API (b)(4)) as the ones validated (b)(4) and 2) the precision and accuracy of calibration standards and QCs in the fasting and fed

¹⁵ GS Review: ANDA 213719, New/ANDA, 7/8/2019 (Module 5.3.1.4. BA18086532...\appendix-b-mvr-sop... and\appendix-c-mvr-sop, which is the same as Module 5.3.1.4. BA17861024-01...\appendix-b-mvr-sop... and\appendix-c-mvr-sop)

studies met the acceptance criteria. Therefore, the assessor will not pursue this issue further.

- According to the method validation report, the prepared calibration standards and QCs were composed of combined sacubitril and valsartan. For stability studies such as processed stability, freeze-thaw stability and long term stability, in addition to evaluating stability of the aforementioned QCs, the applicant also evaluated stability of QCs fortified with metabolite sacubitrilat LBQ657 and 4-hydroxy valsartan (6.000/12.00 µg/mL) (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). It is noted that the concentration of metabolite added (6.000/12.00 µg/mL) is reasonable since it is the same as ULOQ of the parent drug concentration.

The applicant also cross validated for quantitation of sacubitril and valsartan in presence of LBQ657 and 4-hydroxy valsartan. The intra-run precision and accuracy for QC samples of sacubitril and valsartan fortified with LBQ657 and 4-hydroxy valsartan (6.000/12.00 µg/mL) met the acceptance criteria.

3.5 In Vivo Studies

3.5.1 Summary of Fasting Study # BA18086532 (97 mg/103 mg Strength)

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 (% CV)						Study Report Location
					C _{max} (µg/mL)	T _{max} (hr)	AUC _{0-t} (µg*hr/mL)	AUC _∞ (µg*hr/mL)	T _{1/2} (hr)	K _{el} (hr ⁻¹)	
Study # BA18086532	- To compare and evaluate the oral bioavailability of Sacubitril and Valsartan Tablets 97 mg/103 mg with that of ENTRESTO™ (Sacubitril and Valsartan) Tablets 97 mg/103 mg in healthy, adult, human subjects under fasting conditions. - To monitor the safety of the subjects.	An open label, randomized, four-period, two-treatment, two-sequence, fully replicate, single-dose, crossover, balanced, fasting, study design.	Test Product T: Sacubitril / Valsartan Tablets 97 mg /103 mg, 1 × 97 mg / 103 mg, Oral, [Batch No.: ME80350 (Mother Batch # ME80346)] Reference Product R: Entresto™ (Sacubitril / Valsartan) Tablet 97 mg/103 mg, 1 × 97 mg / 103 mg, Oral, [Lot No.: FX000024]	34 dosed, 24 completed study (24 males) Age: 35 (21-43) years Healthy male subjects.	2.061 ±1.039 (50.410)	0.500 (0.333-2.667)	2.574 ±0.697 (27.094)	2.602 ±0.693 (26.650)	0.793 ±0.269 (33.942)	0.948 ±0.247 (26.067)	Module 5.3.1.2

Applicant's Notes: The mean age is calculated based on completed subjects. T_{max} is presented as Median (Range).

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 (%CV)						Study Report Location
					C _{max} (µg/mL)	T _{max} (hr)	AUC _{0-t} (µg*hr/mL)	AUC _∞ (µg*hr/mL)	T _{1/2} (hr)	K _{el} (hr ⁻¹)	
Study # BA18086532	- To compare and evaluate the oral bioavailability of Sacubitril and Valsartan Tablets 97 mg/103 mg with that of ENTRESTO™ (Sacubitril and Valsartan) Tablets 97 mg/103 mg in healthy, adult, human subjects under fasting conditions. - To monitor the safety of the subjects.	An open label, randomized, four-period, two-treatment, two-sequence, fully replicate, single-dose, crossover, balanced, fasting, study design.	Test Product: Sacubitril / Valsartan Tablets 97 mg /103 mg, 1 × 97 mg / 103 mg, Oral, [Batch No.: ME80350 (Mother Batch # ME80346)] Reference Product: Entresto™ (Sacubitril / Valsartan) Tablet 97 mg/103 mg, 1 × 97 mg / 103 mg, Oral, [Lot No.: FX000024]	34 dosed, 24 completed study (24 males) Age: 35 (21-43) years Healthy male subjects.	5.440 ±1.952 (35.879)	1.750 (1.250-4.000)	33.963 ±13.579 (39.983)	34.542 ±13.999 (40.527)	8.091 ±2.305 (28.489)	0.092 ±0.026 (28.242)	Module 5.3.1.2

Applicant's Notes: The mean age is calculated based on completed subjects. T_{max} is presented as Median (Range).

3.5.2 Summary of Fed Study # BA17861024-01 (97 mg/103 mg Strength)

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 (%CV)						Study Report Location
					C _{max} (µg/mL)	T _{max} (hr)	AUC ₀₋₄ (µg*hr/mL)	AUC _∞ (µg*hr/mL)	T _{1/2} (hr)	K _{el} (hr ⁻¹)	
Study # BA17861024-01	- To compare and evaluate the oral bioavailability of Sacubitril and Valsartan Tablets 97 mg/103 mg with that of ENTRESTO™ (Sacubitril and Valsartan) Tablets 97 mg/103 mg in healthy, adult, human subjects under fed conditions. - To monitor the safety of the subjects.	An open label, randomized, two-period, two-treatment, two-sequence, single-dose, crossover, balanced, fed, study design.	Test Product: Sacubitril / Valsartan Tablets 97 mg /103 mg 1 x 97 mg / 103 mg, Oral, [Batch No.: ME80350 (Mother Batch # ME80346)] Reference Product: Entresto™ (Sacubitril / Valsartan) Tablet 97 mg/103 mg 1 x 97 mg / 103 mg, Oral, [Lot No.: FX000024]	38 dosed, 36 completed study (36 males) Age: 31 (20-42) years Healthy male subjects.	1.729 ±0.788 (45.570)	1.750 (0.833-4.500)	2.480 ±0.733 (29.574)	2.507 ±0.735 (29.299)	0.867 ±0.309 (35.639)	0.880 ±0.253 (28.703)	Module 5.3.1.2

Applicant's Notes: The mean age is calculated based on completed subjects. T_{max} is presented as Median (Range).

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 (%CV)						Study Report Location
					C _{max} (µg/mL)	T _{max} (hr)	AUC _{0-t} (µg*hr/mL)	AUC _∞ (µg*hr/mL)	T _{1/2} (hr)	K _{el} (hr ⁻¹)	
Study # BAI7861024-01	- To compare and evaluate the oral bioavailability of Sacubitril and Valsartan Tablets 97 mg/103 mg with that of ENTRESTO™ (Sacubitril and Valsartan) Tablets 97 mg/103 mg in healthy, adult, human subjects under fed conditions. - To monitor the safety of the subjects.	An open label, randomized, two-period, two-treatment, two-sequence, single-dose, crossover, balanced, fed, study design.	Test Product: Sacubitril / Valsartan Tablets 97 mg/103 mg 1 x 97 mg / 103 mg, Oral, [Batch No.: ME80350 (Mother Batch # ME80346)] Reference Product: Entresto™ (Sacubitril / Valsartan) Tablet 97 mg/103 mg 1 x 97 mg / 103 mg, Oral, [Lot No.: FX000024]	38 dosed, 36 completed study (36 males) Age: 31 (20-42) years Healthy male subjects.	2.708 ±0.786 (29.009)	3.000 (1.500-5.000)	17.575 ±6.552 (37.281)	17.913 ±6.614 (36.925)	6.860 ±2.025 (29.524)	0.111 ±0.035 (31.722)	Module 5.3.1.2

Applicant's Notes: The mean age is calculated based on completed subjects. T_{max} is presented as Median (Range).

4 APPENDIX

4.1 Individual Study Assessments

4.1.1 Single-Dose Fasting Bioequivalence Study

4.1.1.1 Study Design

4.1.1.1.1 Study Information

Study Number	BA18086532	
Study Title	Single dose oral bioequivalence study of Sacubitril and Valsartan Tablets 97 mg/103 mg and 'ENTRESTO™' (Sacubitril and Valsartan) Tablets 97 mg/103 mg in healthy adult human subjects under fasting conditions.	
Clinical Site (Name & Address)	Cliantha Research Limited 1 st floor, Silver Arcade, Near Ashwamegh III, Samrajya, Mujmahuda Road, Akota, Vadodara-390020, Gujarat, India	
Principal Clinical Investigator	Dr. Butesh Sakaria, MBBS	
Dosing Dates[^]	Period 1: 1/24/2019 Period 2: 1/31/2019 Period 3: 2/7/2019 Period 4: 2/14/2019	
Analytical Site (Name & Address)	(b)(4)	
Analysis Dates[*]	2/19/2019 to 3/3/2019	
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)	(a) 38 days from 1/24/2019 to 3/3/2019 (For Sacubitril and Valsartan) (b) -20°C ± 10°C temperature (For Sacubitril and Valsartan)	
Long-Term Storage Stability (LTSS) Coverage (no. days @ temp °C)	97 days at -20°C ± 10°C temperature (For Sacubitril and Valsartan) 98 days at -20°C ± 10°C temperature [For Sacubitril and Valsartan fortified with Metabolite Sacubitrilat (LBQ657) and 4-Hydroxy Valsartan (6.000/12.00 µg/mL)]	

[^] Assessor added based on the study report.

^{*} Assessor added based on the bioanalytical report.

4.1.1.1.2 Product (Bio-batch) Information

Product	Test	RLD
Treatment ID	T	R
Product Name	Sacubitril/Valsartan Tablets, 97 mg/103 mg	Entresto™ (Sacubitril / Valsartan) Tablets, 97 mg/103 mg
Manufacturer	(b)(4)	Distributed By: Novartis Pharmaceuticals Corp, East Hanover, NJ 07936 (b)(4)
Batch/Lot No.	ME80350 (Mother Batch # ME80346)	FX000024
Manufacture Date	Dec, 2018	
Expiration Date		May, 2020
Strength	97 mg/103 mg	97 mg/103 mg
Dosage Form	Tablets	Tablets
Bio-Batch Size		
Production Batch Size	(b)(4)	
Potency (Assay)	Sacubitril: 101.0% Valsartan: 98.8%	Sacubitril: 101.2% Valsartan: 99.1%
Content Uniformity (expressed as mean, %CV or per USP)	Sacubitril: Mean: 100.2 %; % CV: 1.29% Valsartan: Mean: 98.8 %; %CV: 1.25%	Sacubitril: Mean: 102.4 %; AV: 2.5 Valsartan: Mean: 101.0 %; AV: 1.5
Dose Administered	1 × (97 mg / 103 mg) Tablet	1 × (97 mg / 103 mg) Tablet
Route of Administration	Oral	Oral

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

4.1.1.1.3 Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	Enrolled: 34 (+3 extra subjects in order to compensate for any dropouts prior to dosing in Period 1) Dosed: 34 Completed: 24 Samples Analyzed: 34 Statistically Analyzed: 24
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	Pre-dose (0.000 hour, collected within 2 hours before dosing) and at 0.167, 0.333, 0.5, 0.667, 0.833, 1.0, 1.25, 1.5, 1.75, 2.0, 2.333, 2.667, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0, 36.0 and 48.0 hours post-dose All samples were analyzed for sacubitril and valsartan. ¹⁶ Concentration data from 0 to 12 hrs was included in the pharmacokinetic and statistical analysis for sacubitril; and concentration data from 0 to 48 hrs was included in the pharmacokinetic and statistical analysis for valsartan. Please see details in assessor's comments below.
IRB Approval	☒ Yes Date: 1/9/2019 ☐ No
Informed Consent	☒ Yes Date: 1/9/2019 ☐ No
Length of Fasting	At least 10 hrs before dosing and at least 4 hrs after dosing
Length of Confinement	At least 11 hrs before dosing until at least 24 hours after dosing
Was the drug product administered per labeling for specialized dosage forms e.g. ODT)?	☐ Yes ☐ No ☒ N/A
Safety Monitoring	☒ Yes ☐ No

¹⁶ According to the study protocol [GS Review: ANDA 213719, New/ANDA, 7/8/2019 (Module 5.3.1.2. BA 18086532...\Protocol or Amendment\fasting-protocol-and-amendments, p. 38 of 114], “[a]ll available samples will be analyzed (If any subject is discontinued and no post dose samples are collected, then pre-dose samples of that period of such subject would not be analyzed)... Concentration data of all subjects who complete all the periods of the study will be included in the pharmacokinetic and statistical analysis.”

Comments on Study Design: Adequate

- The current product-specific guidance (PSG) draft (recommend Apr 2016) for Sacubitril; Valsartan Tablet recommends single-dose, two-way crossover, in-vivo fasting and fed studies. The applicant submitted a single-dose, randomized, 2-treatment, **4-period, fully-replicate**, crossover fasting study. Although the applicant's study design is different from the PSG recommendation, the assessor deems it is acceptable because 1) the applicant's pilot fasting study showed highly variable C_{max} of Sacubitril (CV% of C_{max}: 37.97%) and the applicant pre-established a fully-replicate study design before conducting the pivotal fasting BE study; 2) Office of Research and Standards (ORS)'s responses to controlled correspondence 24442067 and 23610606 state that Office of Generic Drugs (OGD) may accept a single-dose, randomized, four-way, fully-replicated crossover BE study design for Sacubitril and Valsartan Tablet if the applicant provides evidence of high variability in the PK parameters C_{max} and/or AUC (i.e., WSV ≥ 30%) of the reference product^{17,18}.
- The applicant collected blood samples at pre-dose (0.000 hour) and at 0.167, 0.333, 0.5, 0.667, 0.833, 1.0, 1.25, 1.5, 1.75, 2.0, 2.333, 2.667, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0, 36.0 and 48.0 hours post-dose. The applicant stated that considering the half life of sacubitril is ~1 hr, up to 12 hrs time point is sufficient to calculate adequate PK parameters, hence up to 12 hrs time point were utilized to calculate PK parameters for sacubitril. The applicant stated that additional concentration of remaining time points (16, 24, 36, and 48 hrs) for sacubitril were for information only. According to the concentration data reported in the study report¹⁹, the concentration data for time points from 10 to 48 hrs are all 0 for all subjects.

Per RLD labeling, peak plasma concentration of sacubitril and valsartan are reached in 0.5 hrs and 1.5 hrs, respectively; and the half-lives of sacubitril and valsartan are 1.4 hours and 9.9 hrs, respectively. Therefore, the applicant's blood sample collection time should be able to adequately capture the T_{max} (C_{max}) and elimination phase for sacubitril and valsartan. Washout for 7 days between periods is sufficient to ensure the adequate elimination of remaining sacubitril and valsartan before the next dosing period.

¹⁷ GDRP, Controlled correspondence 24442067, C24442067 Review.docx, final date: 10/26/2018
<http://panorama.fda.gov/project/view?ID=5b46483401c76808e64cecf9dba1fab0>

¹⁸ GDRP, Controlled correspondence 23610606, C23610606 Review.docx, final date: 09/27/2018
<http://panorama.fda.gov/project/view?ID=5b1a7cc4005f093c35083dc9568c240d>

¹⁹ GS Review: ANDA 213719, New/ANDA, 7/8/2019 (Module 5.3.1.2. BA 18086532...\Study Report Body\fasting-study-report, p. 65-66 of 130).

4.1.1.2 Clinical Results

4.1.1.2.1 Demographic Profile of Subjects

		Fasting Bioequivalence Study No. BA18086532	
		Treatment Groups	
		Test Product N = 24	Reference Product N = 24
Age (years)	Mean ± SD	35 ± 6	35 ± 6
	Range	21 - 43	21 - 43
Age Groups	< 18	0 (0.00%)	0 (0.00%)
	18 – 40	18 (75.00%)	18 (75.00%)
	41 – 64	6 (25.00%)	6 (25.00%)
	65 – 75	0 (0.00%)	0 (0.00%)
	> 75	0 (0.00%)	0 (0.00%)
Sex	Male	24 (100.00%)	24 (100.00%)
	Female	0 (0.00%)	0 (0.00%)
Race	Asian	24 (100.00%)	24 (100.00%)
	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	24.0 ± 2.8	24.0 ± 2.8
	Range	19.5 – 29.8	19.5 – 29.8
Tobacco Users/Smokers	Yes	0 (0.00%)	0 (0.00%)
	No	24 (100.00%)	24 (100.00%)

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?
(b)(6)	Reason: Withdrew consent for further participation from the study. Date: Time: 08:45 hours Last Treatment Received: NA	NA	Yes [replaced with Extra Subject # and allotted same subject#
	Reason: Withdrew consent for further participation from the study. Date: Time: 08:46 hours	NA	Yes [replaced with Extra Subject #

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(b)(6)	Last Treatment Received: NA		(b)(6)
	Reason: Protocol Violation (Found Positive during alcohol breath test on check-in day of Period-III) Date: Time: 12:11 hours Last Treatment Received: Test	Period II	No
	Reason: Protocol Violation (Found Positive during alcohol breath test on check-in day of Period-II) Date: Time: 12:45 hours Last Treatment Received: Test	Period I	No
	Reason: Did not report for subsequent periods of the study Date: Time: 07:14 hours Last Treatment Received: Test	Period II	No
	Reason: Protocol Violation (Found BZD Positive during urine scan for drugs of abuse on check-in day of Period-III) Date: Time: 12:33 hours Last Treatment Received: Reference	Period II	No
	Reason: Did not report for subsequent periods of the study Date: Time: 07:16 hours Last Treatment Received: Reference	Period II	No
	Reason: Protocol Violation (Found THC Positive during urine scan for drugs of abuse on check-in day of Period-II) Date: Time: 11:54 hours Last Treatment Received: Reference	Period I	No
	Reason: Protocol Violation (Found Positive during alcohol breath test on check-in day of Period-III) Date: Time: 14:41 hours Last Treatment Received: Reference	Period II	No
	Reason: Did not report for subsequent periods of the study Date: Time: 07:18 hours Last Treatment Received: Test	Period II	No
	Reason: Did not report for subsequent periods of the study Date: Time: 07:30 hours Last Treatment Received: Reference	Period I	No

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Single-Dose Fasting Bioequivalence Study Assessment

(b)(6)	Reason: Protocol Violation (Found Positive during alcohol breath test on check-in day of Period-II) Date: Time: 15:48 hours Last Treatment Received: Test	Period I	No

Are dropouts appropriate? If no, please comment.	☒ Yes, the assessor verified the information from the case report form (CRF) ☐ No

4.1.1.2.3 Study Adverse Events

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Fasting Bioequivalence Study No. BA18086532	
	Test (N=32*)	Reference (N=32#)
Investigation		
White blood cell count increased	0 (0.00%)	1 (3.13%)
Lymphocyte count decreased	0 (0.00%)	1 (3.13%)
Total	0 (0.00%)	1 (3.13%)

Applicant's Note:

*24 subjects were dosed twice with Test product in two different periods and 8 subjects were dosed with Test product only once in either of the periods.

24 subjects were dosed twice with Reference product in two different periods and 8 subject was dosed with Reference product only once in either of the periods.

Were subjects who experienced vomiting included in statistical analysis?	☐ Yes ☐ No ☒ N/A
If yes, does the time of emesis exceed two times the median Tmax value (IR products) or the labeled dosing interval (MR products)? Please comment.	☐ Yes ☐ No ☒ N/A
Was the adverse event profile observed comparable for the test and reference product?	☒ Yes ☐ No
Are there any serious adverse events or death?	☐ Yes ☒ No
If yes, then if the study conducted in US, are they reported to the OGD Safety Committee?	☐ Yes ☐ No ☒ N/A
Are there any other safety concerns based on the adverse event profile?	☐ Yes ☒ No

Assessor's Comments:

- Both adverse events (AEs) during the study were considered mild in severity, and unlikely related to the study treatment. All symptoms of AEs reported during the study were resolved.
- No concomitant medication was administered.

4.1.1.2.4 Protocol Deviations

Type	Subject #s (Test)	Subject #s (Ref.)
Blood sample collection time deviations, Period-I	(b)(6)	
Missing Blood Sample deviations, Period-I		
Blood sample collection time deviations, Period-II		
Missing Blood Sample deviations, Period-II		
Blood sample collection time deviations, Period-III		
Missing Blood Sample deviations, Period-III		
Blood sample collection time deviations, Period-IV		
Missing Blood Sample deviations, Period-IV		
Post study safety assessment could not be performed and the subject was declared as lost to follow-up.		

Applicant's Note: Superscript above the subject number indicates the number of multiple occurrences of the indicated deviation recorded by that subject.

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

- There are sampling time deviations in multiple subjects. The applicant used the actual sampling times for the PK analysis. The assessor considers the handling of sampling time deviations acceptable.
- The other protocol deviations mentioned above do not affect study outcome.

4.1.1.3 Bioanalytical Results

4.1.1.3.1 SOPs dealing with Sample Analysis including Repeat Analysis

SOP No.	Effective Date of SOP	SOP Title
(b)(4)		Sample Analysis
		Sample Reanalysis and Reporting Criteria

All necessary SOPs submitted?	☒ Yes ☐ No

4.1.1.3.2 Sample Analysis Calibration and Quality Control

Fasting Bioequivalence Study No. BA18086532 Sacubitril										
Parameter	Standard Curve Samples									
Concentration (µg/mL)	0.01000	0.02000	0.04000	0.1000	0.3000	0.6000	1.200	2.400	4.800	6.000
Inter day Precision (%CV)	1.7	3.2	3.7	2.6	3.0	4.4	3.1	3.0	3.1	3.7
Inter day Accuracy (%Actual)	97.6	102	104	104	103	102	100	96.2	95.4	96.7
Linearity (R ²)	0.9927689 – 0.9998264									
Linearity Range (µg/mL)	0.01000 – 6.000									
Sensitivity/LOQ (µg/mL)	0.01000									

Parameter	Quality Control Samples Sacubitril				
	LQC	MQC-2	MQC-1	MQC	HQC
Concentration (µg/mL)	0.03000	0.3600	2.100	3.000	4.500
Inter day Precision (%CV)	4.5	3.9	3.8	5.3	3.5
Inter day Accuracy (%Actual)	98.8	101	96.5	93.3	94.9

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 (34 x 20% = 6.8) The applicant provided chromatograms for 8 subjects (Subjects)
Were chromatograms serially or randomly selected?	☒ serially ☐ randomly
Any interfering peaks in chromatogram?	☒ Yes ☐ No Please see assessor's comments below
Were the chromatograms submitted by the applicant acceptable?	☒ Yes ☐ No
Were 100% raw analytical data, including failed runs, provided?	☒ Yes ☐ No

Fasting Bioequivalence Study No. BA18086532 Valsartan										
Parameter	Standard Curve Samples									
Concentration (µg/mL)	0.02000	0.04000	0.08000	0.2000	0.6000	1.200	2.400	4.800	9.600	12.00
Inter day Precision (%CV)	2.0	3.7	3.4	2.5	3.6	4.1	2.5	2.8	2.8	3.3

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Inter day Accuracy (%Actual)	97.9	101	104	104	103	102	100	96.0	95.9	96.3
Linearity (R ²)	0.9911389 – 0.9995644									
Linearity Range (µg/mL)	0.02000 – 12.00									
Sensitivity/LOQ (µg/mL)	0.02000									

Parameter	Quality Control Samples				
	Valsartan				
Concentration (µg/mL)	LQC 0.06000	MQC-2 0.7200	MQC-1 4.200	MQC 6.000	HQC 9.000
Inter day Precision (%CV)	6.0	4.5	4.5	6.5	4.0
Inter day Accuracy (%Actual)	101	102	98.4	93.1	96.1

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 (34 x 20% = 6.8) The applicant provided chromatograms for 8 subjects (Subjects -)
Were chromatograms serially or randomly selected?	☒ serially ☐ randomly
Any interfering peaks in chromatogram?	☒ Yes ☐ No Please see assessor's comments below
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

Sacubitril

Fasting Bioequivalence Study No. BA18086532								
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	0	0	0.00	0.00	0	0	0.00	0.00
Auto injector vial leaked	1	0	0.07	0.00	1	0	0.07	0.00
Above limit of quantitation	1	0	0.07	0.00	1	0	0.07	0.00
Low internal standard	1	3	0.07	0.22	1	3	0.07	0.22
High internal standard	8	6	0.57	0.43	8	6	0.57	0.43
Total	11	9	0.78	0.65	11	9	0.78	0.65

Valsartan

Fasting Bioequivalence Study No. BA18086532								
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	0	0	0.00	0.00	0	0	0.00	0.00
Auto injector vial leaked	1	0	0.07	0.00	1	0	0.07	0.00
Above limit of quantitation	3	0	0.21	0.00	3	0	0.21	0.00
Low internal standard	1	3	0.07	0.22	1	3	0.07	0.22
High internal standard	9	6	0.64	0.43	9	6	0.64	0.43
Total	14	9	0.99	0.65	14	9	0.99	0.65

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
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

Comments for Both Sacubitril and Valsartan

- In addition to the QCs validated in method validation, the applicant also added an additional QC sample (MQC of 3.000 µg/mL and 6.000 µg/mL for sacubitril and valsartan, respectively) for Run 14 (Subject). Prior to adding this MQC, the applicant conducted a new QC validation run, which composed of 6 MQC samples. It is also noted that the precision and accuracy of this MQC is acceptable (please see results in tables in Section 4.1.1.3.2).
- The incurred sample reanalysis (ISR) was performed on 8.31% of the samples (232 out of 2792 total samples). The applicant selected ISR samples near C_{max} and in the elimination phase. Approximately 98.71% (229 out of 232) and 99.57% (231 out of 232) of the ISR were within 20% of the mean of original and repeat results for sacubitril and valsartan, respectively. Therefore, the ISR results met the acceptance criteria (2/3rd of the ISR samples with concentrations within ±20.00% compared to mean of the original analysis and ISR).

Comments for Sacubitril

- Based on the chromatograms provided, there is interference in chromatograms for a few study samples (please see representative chromatograms below). It is noted

that this sample has concentration below LLOQ, hence it is not expected to affect the study outcome. Therefore, the assessor will not pursue this issue further.

Representative chromatograms with interference (Subject [] Period 3, 10 hrs)



Rejected Runs

- The applicant did not report any rejected runs for study samples of sacubitril.

Reinjection

- There are 2 runs that contained reinjected samples (please see summary table below for details). The assessor's evaluation of these reinjections is detailed in the table below.

Run ID	Reinjected Samples		Applicant's Reason for Reinjection	Applicant's Reason for Reinjection per SOP?	Original Injection Data Submitted?	Time interval between the start of the original injection to the end of the final re-injected run	Covered by in-processed stability of 123 hrs at 2-10°C (for both sacubitril and valsartan) as established in pre-study method validation?					
	Subject	Period						Time (hr)				
(b)(6)	1	0-0.833	Leakage occurred at inlet of ion source during acquisition of sample name "____". Hence, run was aborted after completion of the sample name "____". Upon reviewing the result, it was observed that leakage was started from sample name "____" to "____". As a result no desired chromatography was observed between sample name "____" to "____". Upon investigation, it was observed that ferrule (which connects HPLC peak tubing from outlet of column to inlet of ion source) was loose at inlet of ion source which actually resulted into leakage. Furthermore, decreasing pattern for internal standard response observed in Sacubitril and Valsartan. During acquisition of the sample name: "____", "Device fault detected error" was occurred and the mass icon turned red. As a result the run got stopped and subsequent samples (i.e. "____" to "____") of the run were suspended automatically.	Yes	Yes	31.17 hrs	Yes					
								2	0-0.833			
										3	0-0.833	
												4
	1	0		0	Yes	Yes	12.43 hrs	Yes				
									2	0		
											3	0

Repeat Analysis

Auto Injector Vial Leaked

One (1) sample (Subject [REDACTED], Period 3, 0.167 hr) was reassayed due to auto injector vial leaked. According to SOP [REDACTED], samples falling in injection (instrument) related error(s), including auto injector vial leaked, should be repeated in singlet and the repeat value(s) will be reported for final results. Regarding this sample, the applicant stated that no response was observed for internal standard (IS) and insignificant peak area response was observed for sacubitril. Hence, auto injector vial of the sample was checked after completion of the run. Upon checking, minor crack was observed at the bottom of auto injector vial which resulted into leakage. The assessor verified from the raw data that the IS peak area of this sample is 0, and the analyte peak area of this sample is similar to that of the pre-dose sample (IS peak area and analyte peak area for valsartan are both 0), which is consistent with the applicant's claim of auto injector vial leaked. Therefore, the assessor considers the applicant's reason for reassay is in accordance SOP. The final reporting of this sample was also per SOP.

Above Limit of Quantitation

One (1) sample (Subject [REDACTED], Period 3, 0.667 hr) was reassayed due to concentration above limit of quantitation. The assessor verified that reason for reassay is in accordance with the aforementioned SOP [REDACTED]. As per SOP, the original value of this sample (6.107 µg/mL) exceeded the nominal concentration of the highest standard (6.000 µg/mL). This sample was repeated in singlet per SOP, and the reassayed value (after correcting for dilution factor) were greater than the highest standard. The final reporting of this sample was per SOP.

Low/High Internal Standard

Four (4) samples were reassayed due to low internal standard and fourteen (14) samples were reassayed due to high internal standard. According to the aforementioned SOP, "[t]o identify the samples with high or low internal standard, the mean internal standard response will be calculated for the whole batch run. The samples deviating $\pm 40\%$ from the mean will be flagged as High internal standard (HIS) or low internal standard (LIS) respectively."

The assessor has verified from the raw data that IS of the corresponding original sample differed $>40\%$ from the average peak area of the whole batch run. Therefore, the assessor considers that these samples were correctly identified per SOP. The reassayed values were reported as final values per SOP.

Comments for Valsartan

- Based on the chromatograms provided, there is interference in chromatograms for one study sample (please see chromatograms below). It is noted that this sample has concentration below LLOQ, hence it is not expected to affect the study outcome. Therefore, the assessor will not pursue this issue further.

Representative chromatograms with interference (Subject [] Period 3, 48 hrs)



Rejected Runs

- The applicant did not report any rejected runs for study samples of valsartan.

Reinjection

- There are 2 runs that contained reinjected samples. For details, please see summary table and assessor's evaluation in the reinjection section for sacubitril above.

Repeat Analysis

Auto Injector Vial Leaked

One (1) sample (Subject [], Period 3, 0.167 hr) was reassayed due to auto injector vial leaked. This is the same sample that was repeated due to the same reason for sacubitril (please see assessor's comments for sacubitril above). The assessor verified from the raw data that the analyte and IS peak area of this sample are both 0, which is consistent with the applicant's claim of auto injector vial leaked. Therefore, the assessor considers the applicant's reason for reassay is in accordance with SOP. The final reporting of this sample was also per SOP.

Above Limit of Quantitation

Three (3) samples (Subject [], Period 3, 1.25, 1.5 and 1.75 hrs) were reassayed due to concentration above limit of quantitation. The assessor verified that reason for reassay is in accordance with the aforementioned SOP []. As per SOP, the original value of these 3 samples exceeded the nominal concentration of the highest standard (12.00 µg/mL). These samples were repeated in singlet per SOP, and the reassayed values (after correcting for dilution factor) were [] than []% of the highest standard. The final reporting of these samples was per SOP.

Low/High Internal Standard

Four (4) samples were reassayed due to low internal standard and fifteen (15) samples were reassayed due to high internal standard. The assessor has verified from the raw data that IS of the corresponding original sample differed >40% from the average peak area of the whole batch run. Therefore, the assessor considers that these samples were correctly identified per SOP. The reassayed values were reported as final values per SOP.

4.1.1.4 Pharmacokinetic Results

Assessor's Note: In the current submission, the applicant only provided SAS .xpt dataset for subjects that completed all 4 periods of the study, in accordance with their protocol. The applicant will be asked to update their SAS .xpt dataset to also include data from all discontinued subjects. The assessor will analyze data upon receipt of this updated dataset. The applicant's summary tables are provided below for information only.

4.1.1.4.1 Arithmetic Mean Pharmacokinetic Parameters – Applicant's Results

Sacubitril

PARAMETER	Test Product: Sacubitril / Valsartan Tablets 97 mg /103 mg		Reference Product: Entresto™ (Sacubitril / Valsartan) Tablet 97 mg/103 mg	
	N	Arithmetic mean ±Std Deviation (Coeff of Variation (%))	N	Arithmetic mean ±Std Deviation (Coeff of Variation (%))
Cmax (µg/ mL)	48	2.061 ± 1.039 (50.410)	48	2.111 ± 1.019 (48.261)
AUCt (µg/mL)*(hr)	48	2.574 ± 0.697 (27.094)	48	2.590 ± 0.615 (23.756)
AUCi (µg/mL)*(hr)	48	2.602 ± 0.693 (26.650)	48	2.616 ± 0.613 (23.416)
AUC_%Extrap_obs	48	1.174 ± 1.428 (121.671)	48	1.070 ± 1.299 (121.350)
Kel (1/hr)	48	0.948 ± 0.247 (26.067)	48	0.948 ± 0.295 (31.114)
tHalf (hr)	48	0.793 ± 0.269 (33.942)	48	0.816 ± 0.341 (41.787)
Tmax (hr)*	48	0.500 (0.333 - 2.667)	48	0.667 (0.167- 4.000)

* Tmax values are presented as median (range)

Valsartan

PARAMETER	Test Product: Sacubitril / Valsartan Tablets 97 mg /103 mg		Reference Product: Entresto™ (Sacubitril / Valsartan) Tablet 97 mg/103 mg	
	N	Arithmetic mean ±Std Deviation (Coeff of Variation (%))	N	Arithmetic mean ±Std Deviation (Coeff of Variation (%))
Cmax (µg/ mL)	48	5.440 ± 1.952 (35.879)	48	5.247 ± 1.881 (35.855)
AUCt (µg/mL)*(hr)	48	33.963 ± 13.579 (39.983)	48	33.511 ± 11.881 (35.455)

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AUCi (µg/mL)*(hr)	48	34.542 ± 13.999 (40.527)	48	34.052 ± 12.172 (35.746)
AUC_%Extrap_obs	48	1.589 ± 0.991 (62.365)	48	1.578 ± 1.169 (74.076)
Kel (1/hr)	48	0.092 ± 0.026 (28.242)	48	0.096 ± 0.027 (27.810)
tHalf (hr)	48	8.091 ± 2.305 (28.489)	48	7.736 ± 2.198 (28.408)
Tmax (hr)*	48	1.750 (1.250 - 4.000)	48	1.750 (1.000- 5.000)

* Tmax 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 1 x 97 mg/ 103 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasting Bioequivalence Study No. BA18086532							
Sacubitril							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
AUC0-t (hr *µg/ml)	2.491	48	2.523	48	0.9872	95.78	101.75
AUC∞ (hr *µg/ml)	2.521	48	2.551	48	0.9882	95.88	101.85
Cmax (µg/ml)	1.850	48	1.898	48	0.9745	NA	NA
Valsartan							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
AUC0-t (hr *µg/ml)	31.441	48	31.454	48	0.9996	NA	NA
AUC∞ (hr *µg/ml)	31.951	48	31.960	48	0.9997	NA	NA
Cmax (µg/ml)	5.099	48	4.930	48	1.0343	NA	NA

Fasting Bioequivalence Study No. BA18086532								
Sacubitril								
Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	Outcome
LAUCt	NA	95.78%	101.75%	0.0078	0.088	NA	Average Bioequivalence	Bioequivalent
LAUCi	NA	95.88%	101.85%	0.0077	0.088	NA	Average Bioequivalence	Bioequivalent
LCmax	0.97	NA	NA	0.1338	0.366	-0.0672	Scaled Average Bioequivalence	Bioequivalent
Valsartan								
Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	Outcome
LAUCt	1.00	NA	NA	0.1056	0.325	-0.0553	Scaled Average Bioequivalence	Bioequivalent
LAUCi	1.00	NA	NA	0.1032	0.321	-0.0541	Scaled Average	Bioequivalent

							Bioequivalence	
LCmax	1.03	NA	NA	0.1291	0.359	-0.0652	Scaled Average Bioequivalence	Bioequivalent

4.1.1.4.3 Additional Information for the Study

Assessor's Note: As mentioned above, in the current submission, the applicant only provided SAS .xpt datasets for subjects that completed all 4 periods of the study. The following evaluation is based on the current SAS .xpt datasets with subjects that completed all 4 periods of the study, and is subject to change upon receipt of the applicant's updated datasets with the inclusion of discontinued subjects.

Sacubitril

Is there a Tmax difference between Test and Reference? If yes, please provide brief explanation (or detailed explanation, including Tmax analysis, for substantial difference).	☒ Yes ☐ No Please see assessor's comments below
Were the subjects dosed in groups? If yes, was the statistical analysis proper? Is reanalysis by assessor necessary?	☐ Yes ☒ No
Are there measurable drug concentrations at 0 hr? If yes, please comment (and take necessary action, if needed).	☐ Yes ☒ No
Are there first measurable drug concentration as Cmax? If yes, please comment.	☒ Yes ☐ No Please see assessor's comments below
Are there Cmax at the first time point? If yes, is the study (sample) design adequate?	☒ Yes ☐ No Please see assessor's comments below

Valsartan

Is there a Tmax difference between Test and Reference? If yes, please provide brief explanation (or detailed explanation, including Tmax analysis, for substantial difference).	☐ Yes ☒ No Please see assessor's comments below
Were the subjects dosed in groups? If yes, was the statistical analysis proper? Is reanalysis by assessor necessary?	☐ Yes ☒ No
Are there measurable drug concentrations at 0 hr? If yes, please comment (and take necessary action, if needed).	☐ Yes ☒ No
Are there first measurable drug concentration as Cmax? If yes, please comment.	☐ Yes ☒ No
Are there Cmax at the first time point? If yes, is the study (sample) design adequate?	☐ Yes ☒ No

Comments on PK results: Inadequate

- As mentioned above, in the current submission, the applicant only provided SAS .xpt datasets for subjects that completed all 4 periods of the study. The applicant will be asked to update their SAS .xpt datasets to also include data from all discontinued subjects. The assessor will analyze data upon receipt of this updated dataset.
- Based on the current dataset (only included subjects who completed all 4 periods of the study) for sacubitril, 1 subject period (Subject [] Period 3) for the reference product had the first measurable drug concentration as Cmax, and also first post-dose time point as Cmax. However, it should be noted that the applicant included sufficient PK sampling times to cover the expected Tmax range per the RLD labeling (i.e. 0.5 hr and 1.5 hrs for sacubitril and valsartan, respectively). The applicant included early time point (10 minutes) in addition to 5 more time points within the first hour. This time point selection is in line with *Draft Guidance for Industry – Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted under an ANDA* (posted Dec 2013).
- Tmax (hr) for the test and reference product, as provided by the applicant, are summarized below:

Sacubitril

	Test	Reference	Ratio
Median	0.500	0.667	0.75
Min	0.333	0.167	1.99
Max	2.667	4.000	0.67

Valsartan

	Test	Reference	Ratio
Median	1.750	1.750	1.00
Min	1.250	1.000	1.25
Max	4.000	5.000	0.80

It is noted that based on the applicant's results, the Tmax between the test and reference treatment is comparable for valsartan but the ratio is not within 0.8 – 1.25 for sacubitril. Since the assessor will analyze the data upon applicant's updated SAS .xpt datasets with the inclusion of discontinued subjects, the Tmax values listed above is subject to change.

4.1.1.5 Overall Comment

Was the fasting bioequivalence study acceptable? Incomplete

Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Sacubitril - Applicant's Results					
Assessor's Note: As detailed in Section 4.1.1.4, assessor will analyze the data upon receipt of applicant's updated SAS .xpt datasets. The applicant's results are provided below for information only.					
Time (hr)	Test (n= 48)		Reference (n= 48)		T/R Ratio [^]
	Mean (ng/mL)	% CV [^]	Mean (ng/mL)	% CV [^]	
0	0	-	0	-	-
0.167	0.165	144.24	0.217	259.45	0.76
0.333	1.281	71.82	1.256	73.49	1.02
0.5	1.853	57.04	1.667	59.87	1.11
0.667	1.696	61.79	1.664	63.40	1.02
0.833	1.351	53.15	1.437	61.31	0.94
1	1.084	43.91	1.174	59.63	0.92
1.25	0.832	50.24	0.836	57.89	1.00
1.5	0.672	59.38	0.624	60.42	1.08
1.75	0.512	63.67	0.502	64.94	1.02
2	0.375	57.33	0.396	71.97	0.95
2.333	0.279	61.65	0.295	77.97	0.95
2.667	0.284	89.44	0.259	74.52	1.10
3	0.275	101.45	0.236	102.97	1.17
3.5	0.24	95.00	0.232	115.95	1.03
4	0.196	99.49	0.217	126.27	0.90
5	0.087	91.95	0.102	133.33	0.85
6	0.025	92.00	0.03	120.00	0.83
8	0.002	250.00	0.005	220.00	0.40
10	0	-	0	-	-
12	0	-	0	-	-

[^] Assessor calculated based on the applicant's summary data.

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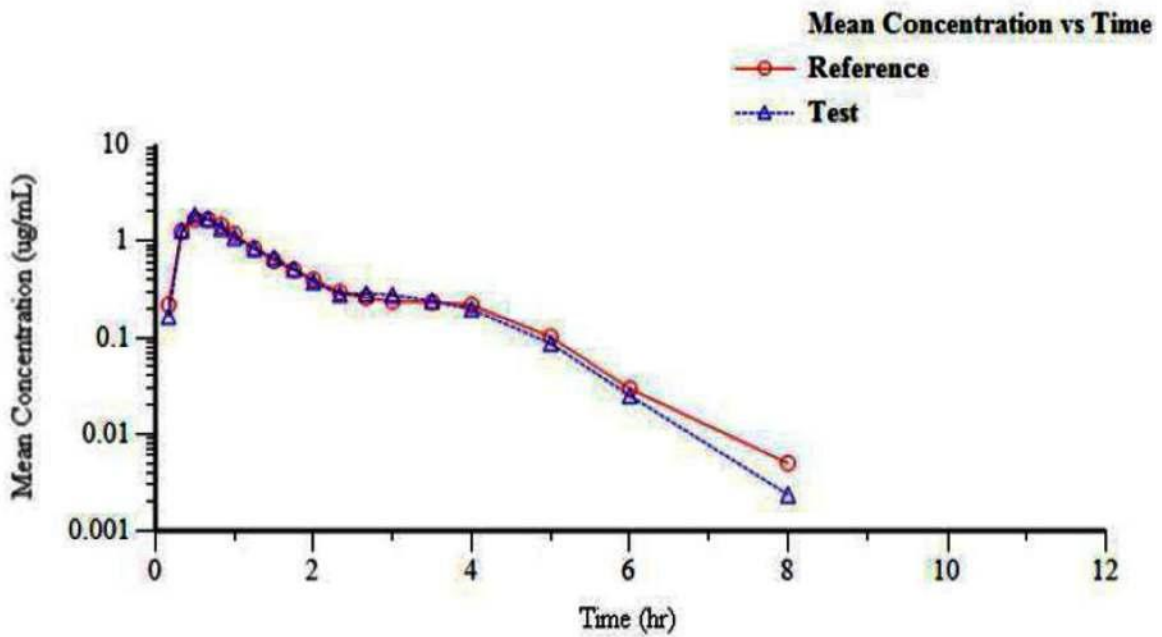
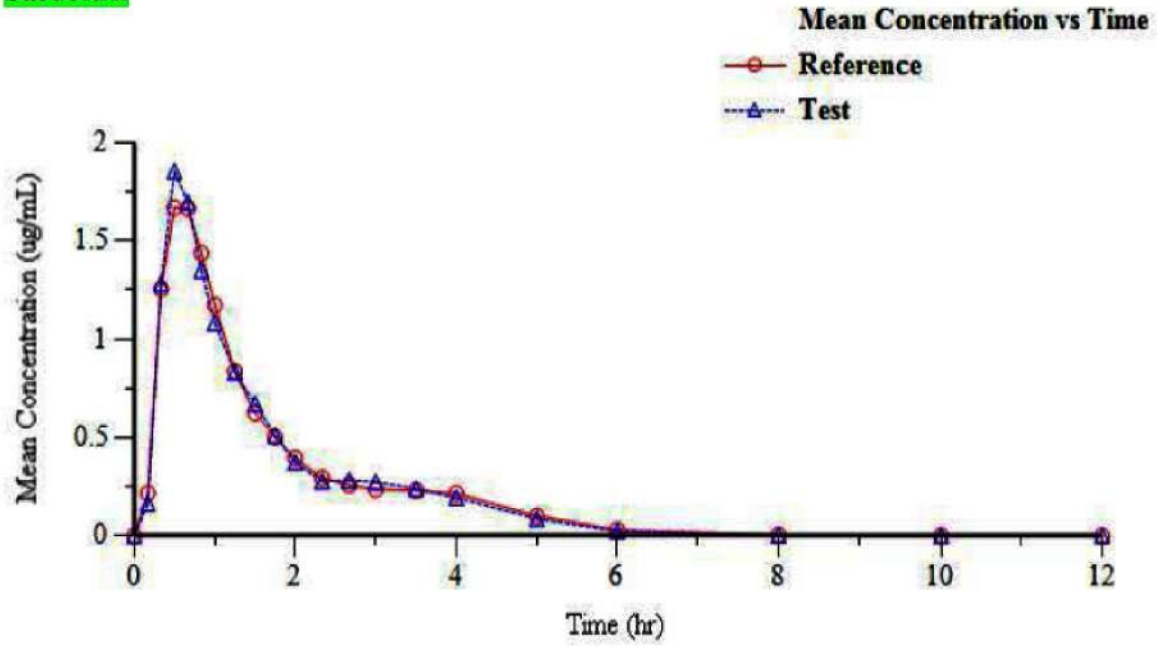
Valsartan - Applicant's Results					
Assessor's Note: As detailed in Section 4.1.1.4, assessor will analyze the data upon receipt of applicant's updated SAS .xpt datasets. The applicant's results are provided below for information only.					
Time (hr)	Test (n= 48)		Reference (n= 48)		T/R Ratio [^]
	Mean (ng/mL)	% CV [^]	Mean (ng/mL)	% CV [^]	
0	0		0		
0.167	0.162	72.84	0.127	66.93	1.28
0.333	0.782	46.80	0.645	41.86	1.21
0.5	1.546	43.53	1.433	39.22	1.08
0.667	2.411	41.68	2.247	39.56	1.07
0.833	3.25	42.25	3.023	37.98	1.08
1	3.877	41.86	3.635	39.28	1.07
1.25	4.646	41.07	4.387	39.80	1.06
1.5	4.913	39.45	4.756	38.31	1.03
1.75	5.006	37.50	4.858	37.22	1.03
2	4.941	36.98	4.771	37.35	1.04
2.333	4.6	38.98	4.582	35.49	1.00
2.667	4.459	36.98	4.323	34.81	1.03
3	4.189	37.14	4.114	33.23	1.02
3.5	4.027	37.99	3.868	31.44	1.04
4	3.813	38.63	3.719	33.23	1.03
5	3.019	42.60	3.016	37.10	1.00
6	2.089	43.94	2.1	39.33	0.99
8	1.339	43.91	1.386	41.77	0.97
10	0.908	44.60	0.939	42.17	0.97
12	0.644	46.58	0.661	43.42	0.97
16	0.352	51.70	0.356	44.94	0.99
24	0.155	67.10	0.153	56.21	1.01
36	0.068	85.29	0.062	74.19	1.10
48	0.022	172.73	0.02	175.00	1.10

[^] Assessor calculated based on the applicant's summary data.

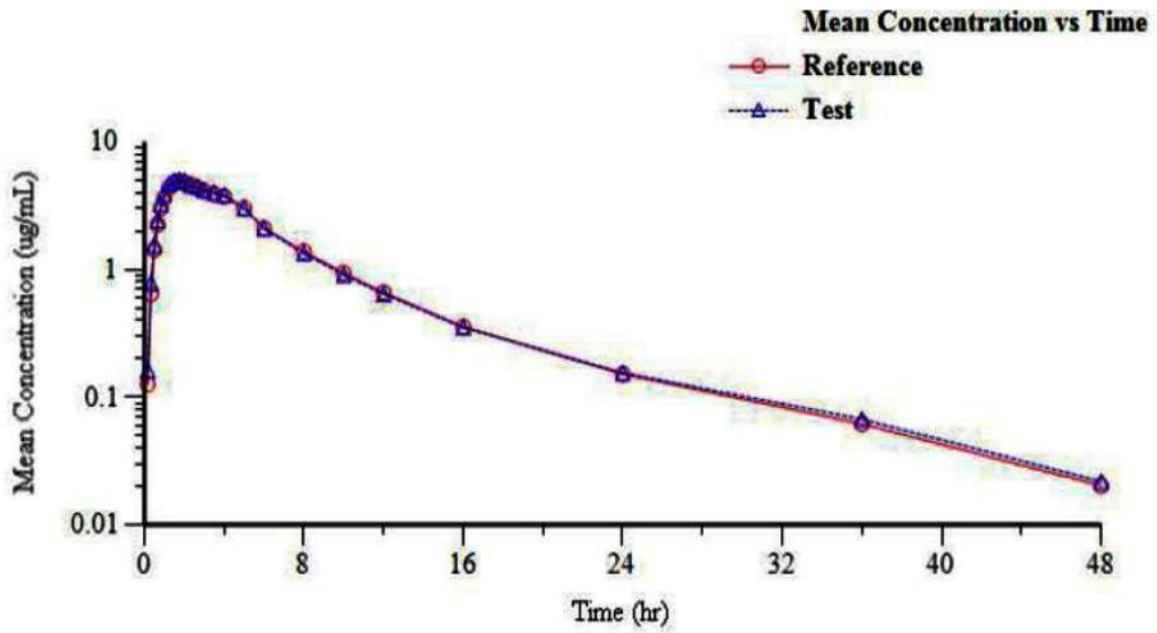
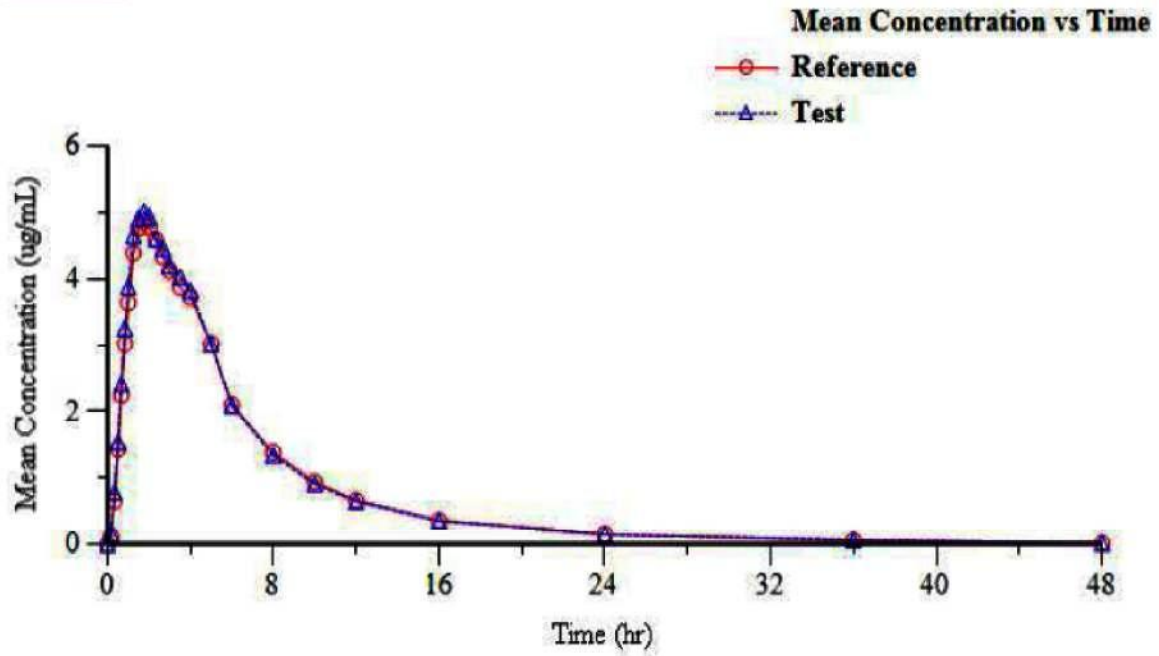
Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study – Applicant's Results

Assessor's Note: As detailed in Section 4.1.1.4, assessor will analyze the data upon receipt of applicant's updated SAS .xpt datasets. The applicant's results are provided below for information only.

Sacubitril



Valsartan



4.1.2 Single-Dose Fed Bioequivalence Study

4.1.2.1 Study Design

4.1.2.1.1 Study Information

Study Number	BA17861024-01	
Study Title	Single dose oral bioequivalence study of Sacubitril and Valsartan Tablets 97 mg/103 mg and 'ENTRESTO™' (Sacubitril and Valsartan) Tablets 97 mg/103 mg in healthy adult human subjects under fed conditions.	
Clinical Site (Name & Address)	Clantha Research Limited 1 st floor, Silver Arcade, Near Ashwamegh III, Samrajya, Mujmahuda Road, Akota, Vadodara-390020, Gujarat, India	
Principal Clinical Investigator	Dr. Virendra Solanki, MBBS	
Dosing Dates[^]	Period 1: 1/31/2019 Period 2: 2/7/2019	
Analytical Site (Name & Address)	(b)(6)	
Analysis Dates*	2/13/2019 to 2/23/2019	
Principal Analytical Investigator	(b)(6)	
Sample Storage: (a) Duration (no. of days from the first day of sample collection to the last day of sample analysis) (b) Temperature Range (e.g., -20°C to -80°C)	(a) 23 days from 31 Jan 19 to 23 Feb 19 (For Sacubitril and Valsartan) (b) -20°C ± 10°C temperature (For Sacubitril and Valsartan)	
Long-Term Storage Stability (LTSS) Coverage (no. days @ temp °C)	97 days at -20°C ± 10°C temperature (For Sacubitril and Valsartan) 98 days at -20°C ± 10°C temperature [for Sacubitril and Valsartan fortified with Metabolite Sacubitrilat (LBQ657) and 4-Hydroxy Valsartan (6.000/12.00 µg/mL)]	

[^] Assessor added based on the study report.

* Assessor added based on the bioanalytical report.

4.1.2.1.2 Product Information

The product information is the same as that used in the fasting study of the same strength. Please refer to Section 4.1.1.1.2 for more information.

4.1.2.1.3 Study Design, Single-Dose Fed Bioequivalence Study

Number of Subjects	Enrolled: 38 (+4 extra subjects in order to compensate for any dropouts prior to dosing in Period 1) Dosed: 38 Completed: 36 Samples Analyzed: 38 Statistically Analyzed: 36
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization	☒ Yes ☐ No
Blood Sampling Times	Pre-dose (0.000 hour, collected within 2 hours before dosing) and at 0.167, 0.333, 0.5, 0.667, 0.833, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0, 36.0 and 48.0 hours post-dose All samples were analyzed for sacubitril and valsartan. ²⁰ Concentration data from 0 to 12 hrs was included in the pharmacokinetic and statistical analysis for sacubitril; and concentration data from 0 to 48 hrs was included in the pharmacokinetic and statistical analysis for valsartan. Please see details in assessor's comments below.
IRB Approval	☒ Yes Date: 1/9/2019 ☐ No
Informed Consent	☒ Yes Date: 1/9/2019 ☐ No
Length of Fasting	At least 10 hours before high-fat high-calorie pre-dose breakfast
Length of Confinement	At least 11 hrs before dosing until at least 24 hours after dosing
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 is listed in the tables below		
Composition of Non-standard FDA Meal Used in Fed Bioequivalence Study		
Composition	Percent	Kcal
Fat	56.537	523.359

²⁰ According to the study protocol [GS Review: ANDA 213719, New/ANDA, 7/8/2019 (Module 5.3.1.2. BA17861024-01... \Protocol or Amendment\fed-protocol-and-amendments, p. 38 of 116], “[a]ll available samples will be analyzed (If any subject is discontinued and no post dose samples are collected, then pre-dose samples of that period of such subject would not be analyzed)... Concentration data of all subjects who complete both periods of the study will be included in the pharmacokinetic and statistical analysis.”

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Carbohydrate		27.245				252.204
Protein		16.218				150.124
Total						925.687
Components of Non-standard FDA Meal Used in Fed Bioequivalence Study						
Ingredients		Amount* (gm)	Energy (kcal)	Protein (kcal)	Fats (kcal)	Carbohydrate (kcal)
Milk (sterilised flavoured)	Milk	250 ml	221.750	32.000	69.750	120.000
	Chicken dana	Chicken	70 gm	120.036	63.336	56.700
	Refined flour	20 gm	69.072	8.288	1.368	59.416
	Oil	20 ml	180.000	0.000	180.000	0.000
Bread butter	Bread	20 gm	49.020	6.24	1.260	41.520
	Butter	10 gm	72.200	0.200	72.000	0.000
Potato chaat	Potato	40 gm	27.116	2.464	0.828	23.824
	Oil	5 ml	45.000	0.000	45.000	0.000
Paneer	Paneer	15 gm	38.713	11.316	19.953	7.444
	Oil	2 ml	18.000	0.000	18.000	0.000
Boiled egg masala	Egg	50 gm	84.780	26.280	58.500	0.000

Applicant's Note: *Quantity of Raw Ingredients

Comments on Study Design: Adequate

- The applicant did not use standard FDA meal. Based on caloric breakdown, the applicant's use of this non-standard meal is acceptable.
- The applicant collected blood samples at pre-dose (0.000 hour) and at 0.167, 0.333, 0.5, 0.667, 0.833, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0, 36.0 and 48.0 hours post-dose. As with the fasting study, the applicant stated that considering the half life of sacubitril is ~1 hr, up to 12 hrs time point is sufficient to calculate adequate PK parameters, hence up to 12 hrs time point were utilized to calculate PK parameters for sacubitril. The applicant stated that additional concentration of remaining time points (16, 24, 36, and 48 hrs) for sacubitril were for information only. According to the concentration data reported in the SAS .xpt dataset, the concentration data for time points from 12 to 48 hrs are all 0 for all subjects.

Per RLD labeling, peak plasma concentration of sacubitril and valsartan are reached in 0.5 hrs and 1.5 hrs, respectively; and the half-lives of sacubitril and valsartan are 1.4 hours and 9.9 hrs, respectively. Therefore, the applicant's blood sample

collection time should be able to adequately capture the Tmax (Cmax) and elimination phase for sacubitril and valsartan. Washout for 7 days between periods is sufficient to ensure the adequate elimination of remaining sacubitril and valsartan before the next dosing period.

4.1.2.2 Clinical Results

4.1.2.2.1 Demographic Profile of Subjects

Fed Bioequivalence Study No. BA17861024-01			
		Treatment Groups	
		Test Product N = 36	Reference Product N = 36
Age (years)	Mean ± SD	31 ± 6	31 ± 6
	Range	20 - 42	20 - 42
Age Groups	< 18	0 (0.00%)	0 (0.00%)
	18 – 40	33 (91.67%)	33 (91.67%)
	41 – 64	3 (8.33%)	3 (8.33%)
	65 – 75	0 (0.00%)	0 (0.00%)
	> 75	0 (0.00%)	0 (0.00%)
Sex	Male	36 (100.00%)	36 (100.00%)
	Female	0 (0.00%)	0 (0.00%)
Race	Asian	36 (100.00%)	36 (100.00%)
	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	22.4 ± 3.2	22.4 ± 3.2
	Range	18.7 – 29.7	18.7 – 29.7
Tobacco Users/Smokers	Yes	0 (0.00%)	0 (0.00%)
	No	36 (100.00%)	36 (100.00%)

Is the demographics profile of subjects completing the bioequivalence study in agreement with the current drug product recommendation?	☒ Yes ☐ No

4.1.2.2 Dropout Information

Subject No.	Reason	Period	Replaced?
(b)(6)	Reason: Withdrew consent for further participation from the study. Date: Time: 08:42 hours Last Treatment Received: NA	NA	Yes (b)(6)
	Reason: Did not report for subsequent period of the study Date: Time: 08:34 hours Last Treatment Received: Reference	Period I	No
	Reason: Withdrawal by subject Date: Time: 16:56 hours Last Treatment Received: Test	Period I	No

Are dropouts appropriate? If no, please comment.	☒ Yes, the assessor verified the information from the CRF ☐ No

4.1.2.2.3 Study Adverse Events

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Fed Bioequivalence Study No. BA17861024-01	
	Test (N=37)	Reference (N=37)
Investigation		
Eosinophil count increased	0 (0.00%)	1 (2.70%)
Total	0 (0.00%)	1 (2.70%)

Were subjects who experienced vomiting included in statistical analysis?	☐ Yes ☐ No ☒ N/A
If yes, does the time of emesis exceed two times the median Tmax value (immediate release products) or the labeled dosing interval (modified release products)? Please comment.	☐ Yes ☐ No ☒ N/A
Was the adverse event profile observed comparable for the test and reference product?	☒ Yes ☐ No
Are there any serious adverse events or death?	☐ Yes ☒ No
If yes, then if the study conducted in US, are they reported to the OGD Safety Committee?	☐ Yes ☐ No ☒ N/A
Are there any other safety concerns based on the adverse event profile?	☐ Yes ☒ No

Assessor's Comments:

- The AE (eosinophil count increased) during the study were considered mild in severity, and unlikely related to the study treatment. All symptoms of AE reported during the study were resolved.
- No concomitant medication was administered.

4.1.2.2.4 Protocol Deviations

Type	Subject #s (Test)	Subject #s (Ref.)
Blood sample collection time deviations, Period-I	(b)(6)	
Missing Blood Sample deviations, Period-I		

Applicant's Note: Superscript above the subject number indicates the number of multiple occurrences of the indicated deviation recorded by that subject.

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

- The applicant stated that Subject was dropped out from the study due to withdrawal by subject. According to the corresponding CRF, this subject "*withdrew his consent for further participation in the study due to some personal reason.*"²¹ No AEs were reported for this subject.
- There are sampling time deviations in multiple subjects. The applicant used the actual sampling times for the PK analysis. The assessor considers the handling of sampling time deviations acceptable.

²¹ GS Review: ANDA 213719, New/ANDA, 7/8/2019 (Module 5.3.1.2. BA17861024-01...Case Report Forms...fed-crf-sub-33, p. 57 of 57).

4.1.2.3 Bioanalytical Results

4.1.2.3.1 SOPs dealing with Sample Analysis including Repeat Analysis

Same as those used in the fasting study for the 97 mg/103 mg strength (please refer to Section 4.1.1.3.1 for more information).

4.1.2.3.2 Sample Analysis Calibration and Quality Control

Fed Bioequivalence Study No. BA17861024-01 Sacubitril										
Parameter	Standard Curve Samples									
Concentration (µg/mL)	0.01000	0.02000	0.04000	0.10000	0.30000	0.60000	1.200	2.400	4.800	6.000
Inter day Precision (%CV)	1.8	3.1	2.2	2.3	1.8	2.5	2.0	1.8	2.7	2.9
Inter day Accuracy (%Actual)	97.9	102	103	103	102	101	99.7	96.7	96.9	97.7
Linearity (R ²)	0.9958174 – 0.9997268									
Linearity Range (µg/mL)	0.01000 – 6.000									
Sensitivity/LOQ (µg/mL)	0.01000									

Parameter	Quality Control Samples Sacubitril				
Concentration (µg/mL)	LQC 0.03000	MQC-2 0.3600	MQC 1.400	MQC-1 2.100	HQC 4.500
Inter day Precision (%CV)	4.0	2.4	2.8	2.7	3.2
Inter day Accuracy (%Actual)	97.6	98.6	93.3	97.3	95.4

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 (38 x 20% = 7.6) The applicant provided chromatograms for 8 subjects (Subjects -)
Were chromatograms serially or randomly selected?	☐ serially ☐ randomly
Any interfering peaks in chromatogram?	☐ Yes ☒ No
Were the chromatograms submitted by the applicant acceptable?	☐ Yes ☒ No
Were 100% raw analytical data, including failed runs, provided?	☒ Yes ☐ No

Fed Bioequivalence Study No. BA17861024-01 Valsartan	
Parameter	Standard Curve Samples

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Concentration (µg/mL)	0.02000	0.04000	0.08000	0.2000	0.6000	1.200	2.400	4.800	9.600	12.00
Inter day Precision (%CV)	1.9	3.4	2.8	2.3	1.9	2.5	2.0	2.0	2.4	2.9
Inter day Accuracy (%Actual)	98.7	101	102	102	102	101	99.6	98.0	96.9	98.6
Linearity (R ²)	0.9957819 – 0.9996626									
Linearity Range (µg/mL)	0.02000 – 12.00									
Sensitivity/LOQ (µg/mL)	0.02000									

Parameter	Quality Control Samples				
	Valsartan				
Concentration (µg/mL)	LQC 0.06000	MQC-2 0.7200	MQC 2.800	MQC-1 4.200	HQC 9.000
Inter day Precision (%CV)	5.2	3.0	3.4	2.9	3.5
Inter day Accuracy (%Actual)	98.8	101	94.9	98.3	96.4

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 (38 x 20% = 7.6) The applicant provided chromatograms for 8 subjects (Subjects -)
Were chromatograms serially or randomly selected?	☒ serially ☐ randomly
Any interfering peaks in chromatogram?	☒ Yes ☐ No Please see assessor's comments below
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

Sacubitril

Fed Bioequivalence Study No. BA17861024-01								
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	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

Valsartan

Fed Bioequivalence Study No. BA17861024-01								
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	0	0	0.00	0.00	0	0	0.00	0.00
Low internal standard	1	0	0.10	0.00	1	0	0.10	0.00
Total	1	0	0.10	0.00	1	0	0.10	0.00

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
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

Comments for Both Sacubitril and Valsartan

- Prior to and during biosample analysis, the applicant conducted a “Pre study_130219” run. According to raw data provided, no biosamples were pre-analyzed in this run.
- In addition to the QCs validated in method validation, the applicant also added an additional QC sample (MQC of 1.400 µg/mL and 2.800 µg/mL for sacubitril and valsartan, respectively) from Run 8 (Subject). Prior to adding this MQC, the applicant conducted a new QC validation run, which composed of 6 MQC samples. It is also noted that the precision and accuracy of this MQC is good (please see results in tables in Section 4.1.2.3.2).
- The ISR was performed on 7.72% of the samples (148 out of 1917 total samples). The applicant selected ISR samples near C_{max} and in the elimination phase. 100% (148 out of 148) of the ISR were within 20% of the mean of original and repeat results for both sacubitril and valsartan. Therefore, the ISR results met the acceptance criteria (2/3rd of the ISR samples with concentrations within ±20.00% compared to mean of the original analysis and ISR).

Comments for Sacubitril

Rejected Runs

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- The applicant reported 2 rejected study sample runs (Run 11 for Subjects [redacted] and Run 14 for Subject [redacted] (b)(6) for sacubitril. Please see assessor's evaluation of this rejected run in the table below.

Run	Subject	Applicant's Reason for Run Rejection	Applicant's Run Rejection per SOP?
11	(b)(6)	Both blank with internal standard samples and both blank without internal standard samples failed to meet in-house SOP acceptance criteria	Yes
14		Both blank without internal standard samples failed to meet in-house SOP acceptance criteria for Sacubitril	Yes

Reinjection

- There is 1 run that contained reinjected samples (please see summary table below for details). The assessor's evaluation of these reinjections is detailed in the table below.

Run ID	Reinjected Samples		Applicant's Reason for Reinjection	Applicant's Reason for Reinjection per SOP?	Original Injection Data Submitted?	Time interval between the start of the original injection to the end of the final re-injected run	Covered by in-processed stability of 123 hrs at 2-10°C (for both sacubitril and valsartan) as established in pre-study method validation?
	Subject	Period					
13	1 and 2	All samples	Leakage was observed at the inlet of ion source during acquisition of the sample name: [redacted]. Hence, the run was suspended after completion of the sample name: [redacted]. Further, due to leakage no chromatography was observed for both analytes and internal standards for samples name: [redacted] and [redacted]. Also, decreasing pattern for both internal standards was observed. Moreover, retention time variation was also observed. Upon investigation, it was observed that HPLC peak tubing which connects column outlet to source inlet was clogged which lead to leakage.	Yes	Yes	21.67 hrs	Yes
	1	0-1.5					
	2	0-1.25					

Repeat Analysis

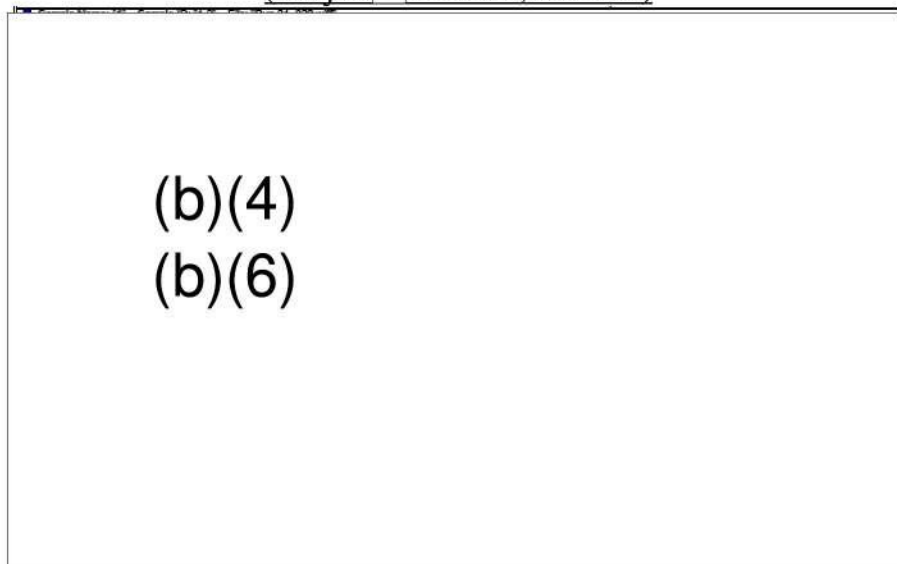
- The applicant stated that no repeat analysis was conducted for sacubitril.

Comments for Valsartan

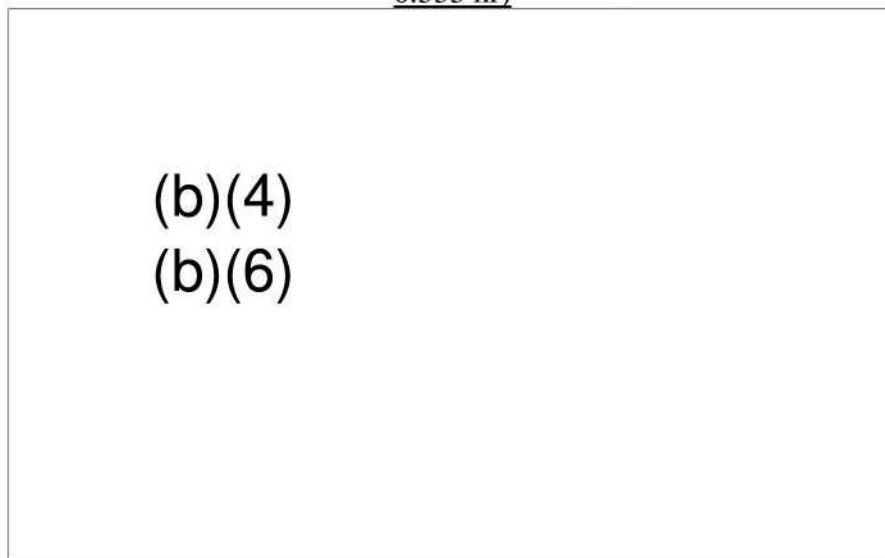
- Based on the chromatograms provided, there is interference in chromatograms for a few study samples (please see representative chromatograms below). It is noted that these samples have concentration below LLOQ and/or have interference <5% of analyte peak area based on visual inspection, hence it is not expected to affect the study outcome. Therefore, the assessor will not pursue this issue further.

Representative chromatograms with interference and concentration below LLOQ

(Subject [] Period 2, 0.167 hr)



Representative chromatograms with interference (concentration above LLOQ, but interference <5% of analyte peak area based on visual inspection (Subject [] Period 1, 0.333 hr)



Rejected Runs

- The applicant did not report any rejected study sample runs for valsartan.

Reinjection

- There is 1 run that contained reinjected samples. For details, please see summary table and assessor's evaluation in the reinjection section for sacubitril above.

Repeat Analysis

Low Internal Standard

One (1) sample was reassayed due to low internal standard. The assessor has verified from the raw data that IS of the corresponding original sample differed >40% from the average peak area of the whole batch run. Therefore, the assessor considers that this sample was correctly identified per SOP. The reassayed value was reported as final value per SOP.

4.1.2.4 Pharmacokinetic Results

4.1.2.4.1 Arithmetic Mean Pharmacokinetic Parameters – Assessor Calculated

Fed Bioequivalence Study No. BA17861024-01									
Sacubitril									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC _{0-t} (hr *ng/mL)	2.480	29.57	0.95	4.39	2.531	30.58	0.97	4.71	0.98
AUC _∞ (hr *µg/mL)	2.506	29.33	0.98	4.42	2.555	30.42	0.99	4.73	0.98
C _{max} (µg/mL)	1.729	45.57	0.41	3.69	1.843	41.44	0.52	4.54	0.94
T _{max} * (hr)	1.750	.	0.83	4.50	1.500	.	0.83	4.50	1.17
Kel (hr ⁻¹)	0.931	31.47	0.40	1.72	0.869	24.09	0.47	1.36	1.07
T _{1/2} (hr)	0.826	35.12	0.40	1.73	0.847	26.70	0.51	1.48	0.97
Valsartan									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC _{0-t} (hr *ng/mL)	17.591	37.25	9.22	34.51	17.141	29.92	9.18	28.92	1.03
AUC _∞ (hr *µg/mL)	17.940	36.93	9.48	35.04	17.540	29.96	9.42	29.41	1.02
C _{max} (µg/mL)	2.708	29.01	1.59	4.42	2.666	24.98	1.60	4.15	1.02
T _{max} * (hr)	3.000	.	1.50	5.00	2.750	.	1.50	4.50	1.09
Kel (hr ⁻¹)	0.107	28.54	0.05	0.18	0.101	28.69	0.06	0.19	1.06

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T1/2 (hr)	7.023	30.17	3.84	14.68	7.381	26.23	3.63	12.04	0.95

* Tmax values are presented as median, range

4.1.2.4.2 Geometric Means and 90% Confidence Intervals - Applicant Calculated

Sacubitril and Valsartan Tablets, 97 mg/ 103 mg 1 x 97 mg/ 103 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fed Bioequivalence Study No. BA17861024-01							
Sacubitril							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
AUC _{0-t} (hr *µg/ml)	2.372	36	2.417	36	0.9816	95.14	101.27
AUC _∞ (hr *µg/ml)	2.401	36	2.442	36	0.9832	95.31	101.43
C _{max} (µg/ml)	1.567	36	1.698	36	0.9226	83.01	102.53
Valsartan							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
AUC _{0-t} (hr *µg/ml)	16.516	36	16.375	36	1.0086	94.16	108.04
AUC _∞ (hr *µg/ml)	16.852	36	16.785	36	1.0040	93.82	107.45
C _{max} (µg/ml)	2.603	36	2.583	36	1.0076	93.93	108.10

4.1.2.4.3 Geometric Means and 90% Confidence Intervals - Assessor Calculated

Sacubitril and Valsartan Tablets, 97 mg/ 103 mg 1 x 97 mg/ 103 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fed Bioequivalence Study No. BA17861024-01							
Sacubitril							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
AUC _{0-t} (hr *µg/ml)	2.37	36	2.42	36	0.98	95.14	101.27
AUC _∞ (hr *µg/ml)	2.40	36	2.44	36	0.98	95.28	101.41
C _{max} (µg/ml)	1.57	36	1.70	36	0.92	83.01	102.53
Valsartan							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
AUC _{0-t} (hr *µg/ml)	16.53	36	16.43	36	1.01	93.86	107.84
AUC _∞ (hr *µg/ml)	16.88	36	16.82	36	1.00	93.73	107.46
C _{max} (µg/ml)	2.60	36	2.58	36	1.01	93.93	108.10

4.1.2.4.4 Additional Information for the Study

Sacubitril

Root Mean Square Error	AUCt: 0.0782 AUCi: 0.0781 Cmax: 0.2651
Is there a Tmax difference between Test and Reference? If yes, please provide brief explanation (or detailed explanation, including Tmax analysis, for substantial difference)	☐ Yes ☒ No
Were the subjects dosed in groups? If yes, was the statistical analysis proper? Is reanalysis by assessor necessary?	☐ Yes ☒ No
Are there measurable drug concentrations at 0 hr? If yes, please comment (and take necessary action, if needed).	☐ Yes ☒ No
Are there first measurable drug concentration as Cmax? If yes, please comment.	☐ Yes ☒ No
Are there Cmax at the first time point? If yes, is the study (sample) design adequate?	☐ Yes ☒ No

Ratio of AUC0-t/AUC _∞				
Treatment	n	Mean	Minimum	Maximum
Test	36	0.99	0.97	1.00
Reference	36	0.99	0.97	1.00
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below.				N/A

Valsartan

Root Mean Square Error	AUCt: 0.1741 AUCi: 0.1714 Cmax: 0.1762
Is there a Tmax difference between Test and Reference? If yes, please provide brief explanation (or detailed explanation, including Tmax analysis, for substantial difference)	☐ Yes ☒ No
Were the subjects dosed in groups? If yes, was the statistical analysis proper? Is reanalysis by assessor necessary?	☐ Yes ☒ No
Are there measurable drug concentrations at 0 hr? If yes, please comment (and take necessary action, if needed).	☐ Yes ☒ No

Are there first measurable drug concentration as C_{max}? If yes, please comment.	☐ Yes ☒ No
Are there C_{max} at the first time point? If yes, is the study (sample) design adequate?	☐ Yes ☒ No

Ratio of AUC _{0-t} /AUC _∞				
Treatment	n	Mean	Minimum	Maximum
Test	36	0.98	0.95	0.99
Reference	36	0.98	0.94	0.99
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below.				N/A

Comments on PK results: Adequate

- The assessor specified linear range used to calculate Kel; therefore, SAS code CALKE was used for statistical analysis.
- T_{max} (hr) for the test and reference product are summarized below:

Sacubitril

	Test	Reference	Ratio
Median	1.75	1.50	1.17
Min	0.83	0.83	1.00
Max	4.50	4.50	1.00

Valsartan

	Test	Reference	Ratio
Median	3.00	2.75	1.09
Min	1.50	1.50	1.00
Max	5.00	4.50	1.11

The assessor considers the T_{max} between the test and reference treatment is comparable for each of sacubitril and valsartan.

- The 90% confidence intervals for sacubitril and valsartan are all within the acceptable limits of 80.00%-125.00%.

4.1.2.5 Overall Comment

Was the Fed bioequivalence study acceptable? Acceptable

Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

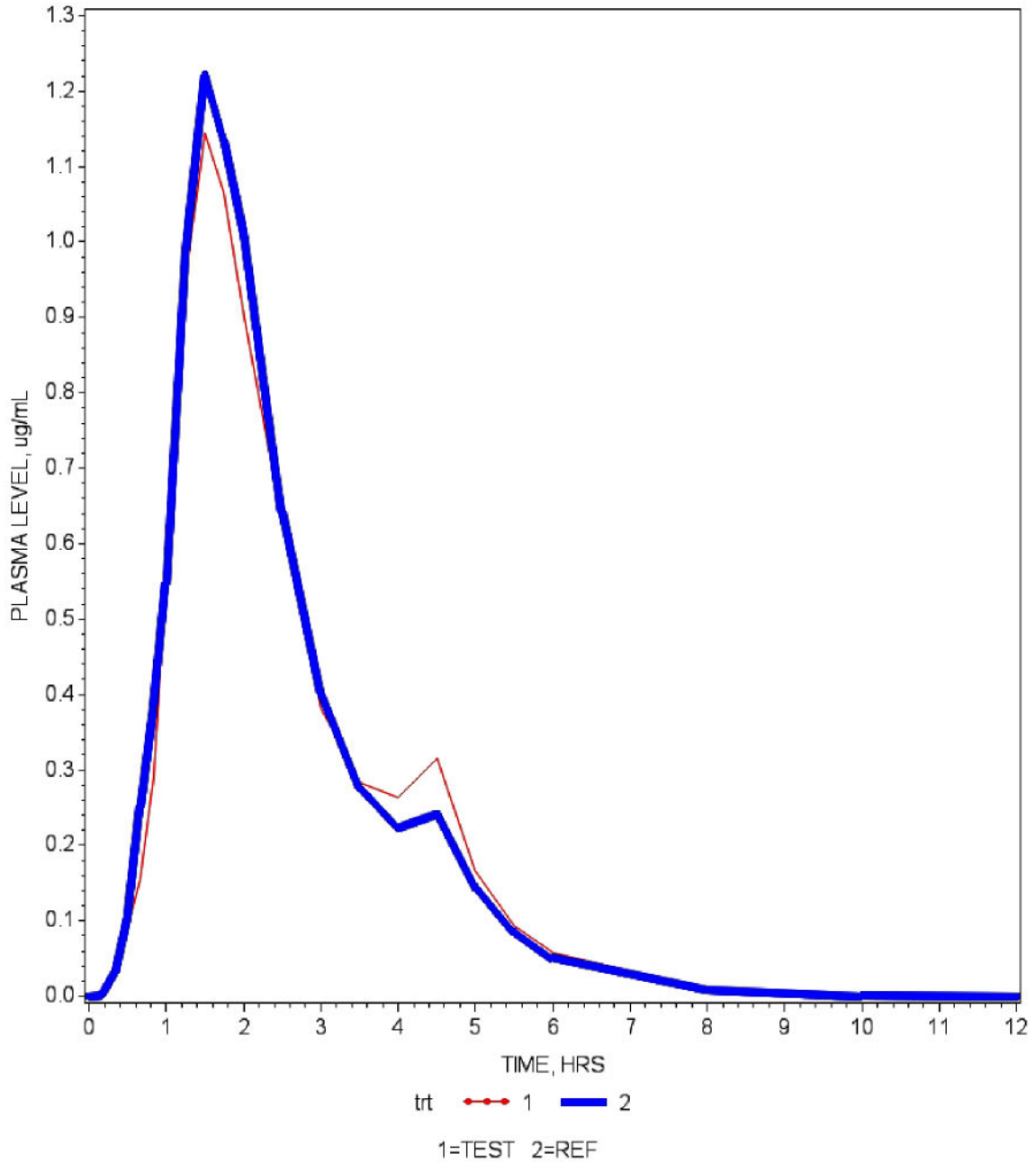
Sacubitril					
Time (hr)	Test (n= 36)		Reference (n= 36)		T/R Ratio
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
0.00	0.00	.	0.00	.	.
0.17	0.00	451.69	0.00	352.49	0.94
0.33	0.04	320.44	0.03	256.42	1.35
0.50	0.09	252.45	0.11	190.54	0.87
0.67	0.15	173.72	0.25	195.67	0.61
0.83	0.29	137.01	0.38	148.53	0.76
1.00	0.55	117.69	0.55	127.51	1.00
1.25	0.96	90.43	0.99	90.91	0.97
1.50	1.14	78.36	1.22	78.17	0.94
1.75	1.06	67.88	1.13	64.15	0.94
2.00	0.90	64.56	1.01	60.68	0.89
2.50	0.63	53.87	0.64	67.09	0.99
3.00	0.38	55.89	0.40	70.47	0.95
3.50	0.28	70.87	0.28	66.52	1.02
4.00	0.26	86.71	0.22	76.02	1.18
4.50	0.32	125.27	0.24	132.40	1.31
5.00	0.17	123.49	0.14	139.42	1.16
5.50	0.09	120.64	0.08	143.20	1.10
6.00	0.06	117.11	0.05	140.05	1.13
8.00	0.01	155.01	0.01	137.40	1.08
10.00	0.00	600.00	0.00	418.29	0.89
12.00	0.00	.	0.00	.	.

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Valsartan					
Time (hr)	Test (n= 36)		Reference (n= 36)		T/R Ratio
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
0.00	0.00	.	0.00	.	.
0.17	0.01	309.20	0.01	268.60	1.28
0.33	0.09	186.00	0.06	187.38	1.63
0.50	0.16	150.19	0.10	141.46	1.66
0.67	0.24	129.25	0.17	102.38	1.41
0.83	0.34	114.52	0.27	93.26	1.24
1.00	0.48	105.38	0.42	94.19	1.16
1.25	0.79	88.94	0.74	79.42	1.06
1.50	1.21	71.42	1.23	70.34	0.98
1.75	1.56	58.99	1.64	60.10	0.95
2.00	1.81	50.21	1.90	48.24	0.95
2.50	2.07	38.57	2.23	33.42	0.93
3.00	2.19	33.94	2.28	28.94	0.96
3.50	2.19	33.96	2.22	27.04	0.99
4.00	2.21	36.11	2.17	28.31	1.02
4.50	2.22	39.78	2.15	29.77	1.04
5.00	1.97	44.87	1.82	30.70	1.08
5.50	1.66	47.56	1.54	31.36	1.08
6.00	1.41	45.85	1.33	31.18	1.06
8.00	0.91	43.94	0.87	31.49	1.04
10.00	0.58	43.38	0.54	32.57	1.09
12.00	0.40	44.11	0.38	33.00	1.04
16.00	0.22	45.56	0.20	39.51	1.07
24.00	0.09	57.22	0.09	57.12	1.02
36.00	0.04	89.62	0.04	72.16	0.93
48.00	0.01	193.06	0.01	218.91	1.07

Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study
Sacubitril

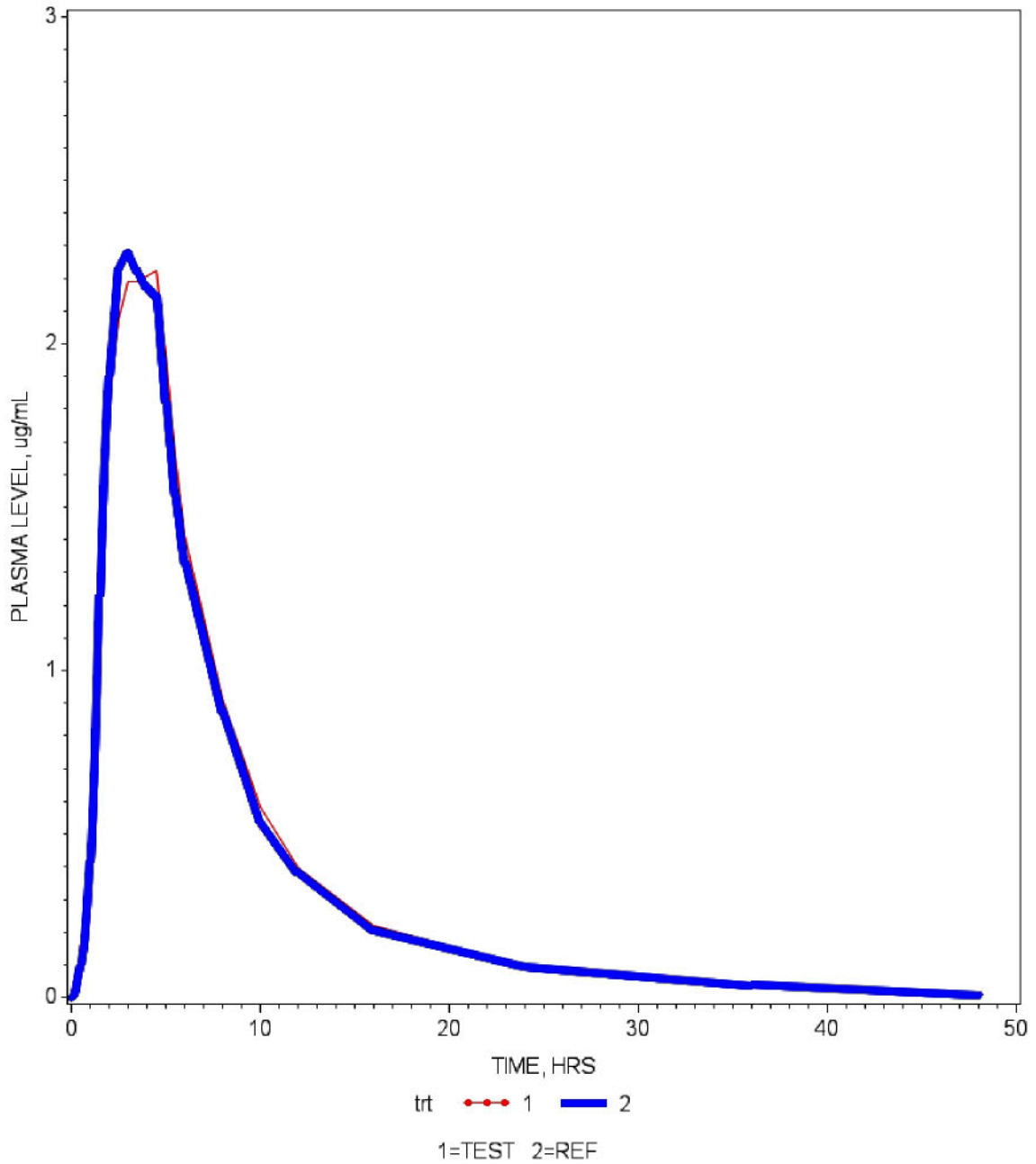
PLASMA Sacubitril LEVELS
Sacubitril and Valsartan Tablets, ANDA 213719
UNDER Fed CONDITIONS
DOSE= 1 x 97 MG/ 103 mg



ANDA 213719
Single-Dose Fed Bioequivalence Study Assessment

Valsartan

PLASMA Valsartan LEVELS
Sacubitril and Valsartan Tablets, ANDA 213719
UNDER Fed CONDITIONS
DOSE= 1 x 97 MG/ 103 mg



4.2 Formulation Data

4.2.1 Test Formulation

Sr. No.	Name of Ingredient	Quantity per Unit (mg)		% w/w**			Function
		24 mg/ 26 mg	49 mg/ 51 mg	97 mg/ 103 mg	24 mg/26 mg	49 mg/51 mg	
1	Sacubitril/Valsartan* [@]						Active ingredient
2	Microcrystalline Cellulose NF			(b)(4)			
3	Low Substituted Hydroxy Propyl Cellulose NF			(b)(6)			
4	Colloidal Silicon Dioxide, NF						(b)(4) (b)(6)
5	Sodium Stearyl Fumarate NF						
Total (Film Coated Tablets)		105.450	210.900	402.000	100.00	100.00	100.00
							-

(b)(4)

(b)(6)

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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) (b)(6)

Amount of Film Coating Ingredients in Each Strength
Ingredients in Opadry

(b)(4)
Iron Oxide Yellow
Iron Oxide Red
Ferrosferric Oxide (b)(4)
(b)(4)
FD&C Yellow #5/ Tartrazine
Aluminum Lake (b)(4)
(b)(4)
FD&C red #40 (b)(4)
aluminum lake (b)(4)
FD&C Blue #2/1 (b)(4)
(b)(4)
(b)(4)

(b)(4)

(b)(4)

4.2.2 RLD Formulation²⁴

Assessor's Note: It is noted that for the strength of 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg as listed in the Orange Book and by the current applicant, the innovator listed the strengths as 50 mg, 100 mg, and 200 mg, respectively.

Table 2-1 Composition of one LCZ696 (sacubitril/valsartan) 50 mg, 100 mg, 200 mg film-coated tablet (mg/ tablet)

Ingredients	Amount (mg) per tablet			Reference to standards
	50 mg ¹	100 mg ²	200 mg ³	
Tablet core				
(b)(4)				(b)(4)
Microcrystalline cellulose				USP/NF / Ph. Eur.
Low Substituted Hydroxypropylcellulose/				USP/NF / Ph. Eur.
Crospovidone,				USP/NF / Ph. Eur.
Magnesium stearate ⁵				USP/NF / Ph. Eur.
Talc				USP/NF / Ph. Eur.
Colloidal silicon dioxide/				USP/NF / Ph. Eur.
(b)(4)				
(b)(4)				
Total Film-coated tablet weight	208.000	208.000	412.000	

(b)(4)

²⁴ The most recent annual report for the RLD product [GS Review: NDA 207620, New/Annual Report, 8/30/2018 (Module 1.13.5) Summary of manufacturing changes, p. 15 and 18 of 18] provided a link to the current RLD formulation, which is GS Review: NDA 207620, New/Annual Report, 8/30/2018 (Module 3.2.P.1) Description and Composition). Therefore, the RLD formulation is extracted from p. 4-6 of 7 of the aforementioned Module 3.2.P.1 document.

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4.2.3 Inactive Ingredients (IIG Table)

Strength	Excipient	Amount (mg)/ Tablet	Amount (mg)/Day	FDA's IIG Limit (mg, Route of Administration) ²⁵	IIG Limit Reference	MDI in Test Formulation Below or Exceeding FDA's IIG Limit
24 mg/26 mg	Microcrystalline Cellulose	(b)(4)	(b)(4)	(b)(4)		Below
	Low Substituted Hydroxy Propyl Cellulose					Below
	Colloidal Silicon Dioxide					Below
	Sodium Stearyl Fumarate					Below
	Crospovidone					Below
24 mg/26 mg	Hypromellose		(b)(4)	(b)(4)		Below
	Titanium Dioxide					Below

²⁵ IIG-MDD_Master Spreadsheet: <http://sharepoint.fda.gov/orgs/CDER-OGD/BIO/IIGMDD%20Master%20Spreadsheet/Forms/AllItems.aspx?InitialTabId=Ribbon%2EDocument&VisibilityContext=WSSSTabPersistence>

49 mg/51 mg	Iron Oxide Yellow	(b)(4)
	Iron Oxide Red	
97 mg/103 mg	FD&C Yellow #5/ Tartrazine Aluminum Lake	(b)(4)
	FD&C Red #40/ Aluminum Lake	
	FD&C Blue #2/ Aluminum Lake	
MDD used for calculation		(b)(4)

(b)(4)

(b)(4)

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Are all strengths of the test product proportionally similar per the BA/BE guidance criteria?	☒ Yes ☐ No ☐ N/A
Are the amounts of all inactive ingredients, based on Maximum Daily Dose (MDD), within IIG (per unit) limits?	☐ Yes ☒ No
If no, are they all within IIG (per day) limits?	☒ Yes ☐ No ☐ N/A
If no, are additional data or Pharm/Tox consult necessary?	☐ Yes ☐ No ☒ N/A
Are all color additives and elemental iron within limits specified by CFR (if applicable) or less than 0.1% of the total unit weight (w/w)?	☒ Yes ☐ No ☐ N/A
Are all strengths of the test formulation acceptable?	☒ Yes ☐ No

Comments on Formulation: Acceptable

- Polyethylene glycol is listed in the internal IIG-MDD database for “pediatric concerns”. The current RLD labeling states that the RLD product is indicated for the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older. Per RLD labeling, the following dosing regimen is recommended for the pediatric population.

	Titration Step Dose (twice daily)		
	Starting	Second	Final
Pediatric Patients Less than 40 kg [†]	1.6 mg/kg	2.3 mg/kg	3.1 mg/kg
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

[†] Use of the Oral Suspension recommended in these patients. Recommended mg/kg doses are of the combined amount of both sacubitril and valsartan [see Dosage and Administration (2.4)].

[†] Doses of 72/78 mg can be achieved using three 24/26 mg tablets [see Dosage Forms and Strengths (3)]

(b)(4)

³⁰ FDA’s Substance Registration System – Unique Ingredient Identifier (UNII): <https://fdasis.nlm.nih.gov/srs/>
Last accessed: 12/10/2019.

(b)(4)

○

○

(b)(4)

None of the excipients are listed in the database for “renal concerns”.

- The test formulation contains FD&C Yellow #5/tartrazine *aluminum lake* for the 97 mg; 103 mg strength, whereas the RLD product does not for any of the 3 strengths. It is noted that FD&C Yellow #5/tartrazine is listed in the internal IIG-MDD database for “general concerns”, with the following comments under “toxicities”:

“FD&C Yellow No. 5 (tartrazine) may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Addition of tartrazine to a drug product adds a significant safety risk of that drug product in susceptible individuals, and therefore this addition is not acceptable in a generic product when the RLD does not contain tartrazine.”

³¹ DailyMed: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a078d9c2-f89c-4f9f-8ded-60ffb2983c3f> Last accessed: 12/18/2019.

(b)(4)

³³ DailyMed: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=51586c47-1aff-4ce6-8030-89f9eb1bc9ac> Last accessed: 12/19/2019.

(b)(4)

“An ANDA that contains tartrazine as an inactive ingredient that requires a warning under FDA’s regulations would be permissible, unless a concern about a particular product has previously been raised by DCR.” (b)(4) “OGDP will work with DLR and DCR on confirming an approach to evaluating when a warning statement on an ANDA would make the product less intrinsically safe and effective than the ANDA’s RLD that reflects current clinical thinking.” It is noted that the currently proposed test product labeling contains a section of “Risk of Allergic Reactions Due to Tartrazine”.³⁵

On 9/4/2019, DBI met with Division of Clinical Review (DCR) and Office of Generic Drug Policy (OGDP) to discuss whether the toxicity concern for FD&C Yellow No. 5/tartrazine is also applicable for FD&C Yellow #5/tartrazine aluminum lake and whether a consult to DCR is needed regarding this issue for the current ANDA. Based on the meeting outcome as well as the post-meeting follow-up notes³⁶, a consult to DCR regarding the aforementioned issue for the current ANDA is not necessary for the current ANDA to establish that the proposed ANDA can contain tartrazine with the required warning because the current ANDA does not raise any unique safety issues with respect to tartrazine. In addition, Division of Labeling Review (DLR) states that it was DLR’s practice to treat “FD&C Yellow #5 tartrazine aluminum lake” the same as “FD&C Yellow #5 tartrazine”. DLR will ensure the Tartrazine warning statement is in the prescribing information and declared on the container label/carton labeling per 21 CFR 201.20.

- Iron oxide yellow, iron oxide red, (b)(4)

(b)(4)

- The formulations for the 24 mg/26 mg and 49 mg/51 mg strengths are proportionally similar to the 97 mg/103 mg bio-strength of the test product.

(b)(4)

³⁵ GS Review: ANDA 213719, New/ANDA, 7/8/2019 (Module 1.14.2.3\PI.pdf, p. 8 of 29).

³⁶ [\\fda.gov\woc\CDER\OGD\All\OGDS11\DIVISION\BIO\BIO1\DBI meeting minutes\DBI General Meeting Minutes\2019\A213719N000DB-MeetingMinutes01-09042019.pdf](https://www.fda.gov/woc/cder/ogd/all/ogds11/division/bio/bio1/dbi_meeting_minutes/dbi_general_meeting_minutes/2019/A213719N000DB-MeetingMinutes01-09042019.pdf)

4.3 Dissolution Testing

4.3.1 Dissolution Data

4.3.1.1 Dissolution Data – 24 mg/26 mg Strength

4.3.1.1.1 Dissolution Data - Sacubitril/Valsartan Tablets, 24 mg/26 mg [Reference product (Lot: FX000303)] vs. Test product (Batch No.: ME80340)] - Sacubitril

Dissolution Conditions		Apparatus:		(b)(4)								
		Speed of Rotation:	Medium:									
Firm's Proposed Specifications		Volume:		(b)(4)								
		Temperature:										
Dissolution Testing Site (Name, Address)		(b)(4)										
Study Ref No.	Testing Date	Product ID/Batch No. (Reference - Exp. Dt.) (Test - Mfg Dt.)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes)				Study Report Location			
					10	15	20	30		45	60	
Study Report	January 03, 2019	Entresto™ Sacubitril/valsartan tablets, 24 mg/26 mg Batch Number: FX000303 Expiry date: Feb, 2021 Distributed by: Novartis pharmaceuticals corp, East Hanover, NJ07936	24 mg/26 mg, Tablets	12	Mean	65.7	87.4	94.0	95.0	95.8	96.8	Module 2.7.1.2
					Range	(b)(4)						
Study Report	January 03, 2019	Sacubitril/Valsartan Tablets, 24mg/26mg Batch Number: ME80340 Mfg. date: Dec, 2018	24 mg/26 mg, Tablets	12	%CV	8.6	8.2	6.9	4.7	3.4	2.8	Module 2.7.1.2
					Mean	62.3	78.9	88.1	93.5	95.3	96.1	
		(b)(4)			%CV	7.6	5.5	5.4	3.4	2.9		

4.3.1.1.2 Dissolution Data - Sacubitril/Valsartan Tablets, 24 mg/26 mg [Reference product (Lot: FX000303)] vs. Test product (Batch No.: ME80340)] - Valsartan

Dissolution Conditions		Apparatus:		Speed of Rotation:		Medium:		Volume:		Temperature:		
		(b)(4)										
Firm's Proposed Specifications		(b)(4)										
Dissolution Testing Site (Name, Address)		(b)(4)										
Study Ref No.	Testing Date	Product ID/Batch No. (Reference - Exp. Dt.) (Test - Mfg Dt.)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes)				Study Report Location			
Study Report	January 03, 2019	Entresto™ Sacubitril/valsartan tablets, 24 mg/26 mg Batch Number: FX000303 Expiry date: Feb, 2021 Distributed by: Novartis pharmaceuticals corp, East Hanover, NJ07936	24 mg/26 mg, Tablets	12	Mean	10	15	20	30	45	60	Module 2.7.1.2
					Range	(b)(4)						
Study Report	January 03, 2019	Sacubitril/Valsartan Tablets, 24mg/26mg Batch Number: ME80340 Mfg. date: Dec. 2018	24 mg/26 mg, Tablets	12	% CV	8.2	7.8	6.5	4.3	2.9	2.6	Module 2.7.1.2
					Mean	62.6	79.1	88.3	93.6	95.3	96.1	
		(b)(4)			Range	(b)(4)						
					% CV	7.5	5.3	5.3	3.3	2.8	2.9	

4.3.1.1.3 Dissolution Data - Sacubitril/Valsartan Tablets, 24 mg/26 mg [Reference product (Lot: FX000303)] vs. Test product (Batch No.: ME80341)] - Sacubitril

Dissolution Conditions		Apparatus:		(b)(4)		Speed of Rotation:		(b)(4)		Medium:		Volume:		Temperature:			
Firm's Proposed Specifications		(b)(4)															
Dissolution Testing Site (Name, Address)		(b)(4)															
Study Ref No.	Testing Date	Product ID\Batch No. (Reference - Exp. Dt.) (Test - Mfg Dt.)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes)						Mean	Range	%CV	Mean	Range	%CV	Study Report Location
Study Report	January 03, 2019	Entresto™ Sacubitril/valsartan tablets, 24 mg/26 mg Batch Number: FX000303 Expiry date: Feb, 2021 Distributed by: Novartis pharmaceuticals corp, East Hanover, NJ07936	24 mg/26 mg Tablets	12	10	15	20	30	45	60	65.7	87.4	94.0	95.0	95.8	96.8	Module 2.7.1.2
					(b)(4)												
					8.6	8.2	6.9	4.7	3.4	2.8							
					60.2	81.4	92.0	96.5	97.8	97.9							
Study Report	January 03, 2019	Sacubitril/Valsartan Tablets, 24mg/26mg Batch Number: ME80341 Mfg. date: Dec, 2018	24 mg/26 mg Tablets	12	(b)(4)												
					10.9	7.5	5.8	3.0	2.1	1.8							

4.3.1.1.4 Dissolution Data - Sacubitril/Valsartan Tablets, 24 mg/26 mg [Reference product (Lot: FX000303)] vs. Test product (Batch No.: ME80341)] - Valsartan

Dissolution Conditions		Apparatus:		Speed of Rotation:		Medium:		Volume:		Temperature:		Study Report Location	
		(b)(4)											
Firm's Proposed Specifications		(b)(4)										Study Report Location	
Dissolution Testing Site (Name, Address)		(b)(4)										Study Report Location	
Study Ref No.	Testing Date	Product ID/Batch No. (Reference - Exp. Dt.) (Test - Mfg Dt.)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes)						Study Report Location		
Study Report	January 03, 2019	Entresto™ Sacubitril/valsartan tablets, 24 mg/26 mg Batch Number: FX000303 Expiry date: Feb, 2021 Distributed by: Novartis pharmaceuticals corp, East Hanover, NJ07936	24 mg/26 mg, Tablets	12	Mean	66.4	87.7	94.1	95.1	96.5	96.8	Module 2.7.1.2	
					Range	(b)(4)							
Study Report	January 03, 2019	Sacubitril/Valsartan Tablets, 24mg/26mg Batch Number: ME80341 Mfg. date: Dec, 2018	24 mg/26 mg, Tablets	12	%CV	8.2	7.8	6.5	4.3	2.9	8.6	Module 2.7.1.2	
					Mean	60.4	81.6	92.1	96.4	97.7	97.8		
					Range	(b)(4)							
					%CV	10.8	7.3	5.7	3.0	2.1	1.7		

4.3.1.1.5 Dissolution Data - Sacubitril/Valsartan Tablets, 24 mg/26 mg [Reference product (Lot: FX000303)] vs. Test product (Batch No.: ME80342)] - Sacubitril

Dissolution Conditions		Apparatus:		(b)(4)		Study Report Location						
		Speed of Rotation:	Medium:									
Firm's Proposed Specifications		Volume:		(b)(4)		Study Report Location						
		Temperature:										
Dissolution Testing Site (Name, Address)		(b)(4)										
Study Ref No.	Testing Date	Product ID/Batch No. (Reference - Exp. Dt.) (Test - Mfg Dt.)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes)			Study Report Location				
Study Report	January 03, 2019	Entresto™ Sacubitril/valsartan tablets, 24 mg/26 mg Batch Number: FX000303 Expiry date: Feb, 2021 Distributed by: Novartis pharmaceuticals corp, East Hanover, NJ07936	24 mg/26 mg, Tablets	12	10	15	20	30	45	60	Module 2.7.1.2	
					Mean	65.7	87.4	94.0	95.0	95.8		96.8
Study Report	March 04, 2019	Sacubitril/Valsartan Tablets, 24mg/26mg Batch Number: ME80342 Mfg. date: Dec. 2018	24 mg/26 mg, Tablets	12	Range			(b)(4)			Module 2.7.1.2	
					%CV	8.6	8.2	6.9	4.7	3.4		2.8
					Mean	57.6	80.3	91.0	96.9	98.7		99.2
				Range		(b)(4)						
				%CV		16.3	10.8	6.6	4.6	3.2	3.7	

4.3.1.1.6 Dissolution Data - Sacubitril/Valsartan Tablets, 24 mg/26 mg [Reference product (Lot: FX000303)] vs. Test product (Batch No.: ME80342)] - Valsartan

Dissolution Conditions		Apparatus:		Speed of Rotation:		Medium:		Volume:		Temperature:		
				(b)(4)		(b)(4)		(b)(4)		(b)(4)		
Firm's Proposed Specifications		(b)(4)										
Dissolution Testing Site (Name, Address)		(b)(4)										
Study Ref No.	Testing Date	Product ID\Batch No. (Reference - Exp. Dt.) (Test - Mfg Dt.)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes)					Study Report Location		
Study Report	January 03, 2019	Entresto™ Sacubitril/valsartan tablets, 24 mg/26 mg Batch Number: FX000303 Expiry date: Feb, 2021 Distributed by: Novartis pharmaceuticals corp, East Hanover, NJ07936	24 mg/26 mg, Tablets	12	Mean	66.4	87.7	94.1	95.1	96.5	96.8	Module 2.7.1.2
					Range	(b)(4)						
Study Report	March 04, 2019	Sacubitril/Valsartan Tablets, 24mg/26mg Batch Number: ME80342 Mfg. date: Dec. 2018	24 mg/26 mg, Tablets	12	%CV	8.2	7.8	6.5	4.3	2.9	8.6	Module 2.7.1.2
					Mean	57.4	79.8	90.3	96.2	98.0	98.3	
					Range	(b)(4)						
					%CV	16.0	10.7	6.4	4.4	3.2	3.7	

4.3.1.2 Dissolution Data – 49 mg/51 mg Strength

4.3.1.2.1 Dissolution Data - Sacubitril/Valsartan Tablets, 49 mg/51 mg [Reference product (Lot: FX000018)] vs. Test product (Batch No.: ME80343) - Sacubitril

Dissolution Conditions		Apparatus:		Speed of Rotation:		Medium:		Volume:		Temperature:		
		(b)(4)										
Firm's Proposed Specifications		(b)(4)										
Dissolution Testing Site (Name, Address)		(b)(4)										
Study Ref No.	Testing Date	Product ID/Batch No. (Reference - Exp. Dt.) (Test - Mfg Dt.)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes)					Study Report Location		
Study Report	January 04, 2019	Entresto™ Sacubitril/Valsartan tablets, 49 mg/51 mg Batch Number: FX000018 Expiry date: May, 2020^ Distributed by: Novartis pharmaceuticals corp, East Hanover, NJ07936	49 mg/51 mg, Tablets	12	Mean	10	15	20	30	45	60	Module 2.7.1.2
					Range	(b)(4)						
Study Report	January 03, 2019	Sacubitril/Valsartan Tablets, 49 mg/51 mg Batch Number: ME80343 Mfg. date: Dec. 2018	49 mg/51 mg, Tablets	12	% CV	7.4	6.3	6.4	4.3	2.5	2.0	Module 2.7.1.2
					Mean	54.2	72.6	83.3	91.2	94.4	96.0	
					Range	(b)(4)						
					% CV	8.7	8.7	7.2	5.7	4.1	3.2	

(b)(4)

³⁷ GS Review: ANDA 213719, New/ANDA, 7/8/2019 (Module 2.7.1)RLD Certificate of Analysis-49mg/51mg).

4.3.1.2.2 Dissolution Data - Sacubitril/Valsartan Tablets, 49 mg/51 mg [Reference product (Lot: FX000018)] vs. Test product (Batch No.: ME80343)] - Valsartan

Dissolution Conditions		Apparatus:		Speed of Rotation:		Medium:		Volume:		Temperature:		
				(b)(4)		(b)(4)		(b)(4)		(b)(4)		
Firm's Proposed Specifications		(b)(4)										
Dissolution Testing Site (Name, Address)		(b)(4)										
Study Ref No.	Testing Date	Product ID\Batch No. (Reference - Exp. Dt.) (Test - Mfg Dt.)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes)					Study Report Location		
Study Report	January 04, 2019	Entresto™ Sacubitril/valsartan tablets, 49 mg/51 mg Batch Number: FX000018 Expiry date: May, 2020^ Distributed by: Novartis pharmaceuticals corp, East Hanover, NJ07936	49 mg/51 mg, Tablets	12	Mean	58.7	80.0	90.9	95.9	97.3	97.8	Module 2.7.1.2
					Range	(b)(4)						
Study Report	January 03, 2019	Sacubitril/Valsartan Tablets, 49 mg/51 mg Batch Number: ME80343 Mfg. date: Dec. 2018	49 mg/51 mg, Tablets	12	%CV	7.3	6.2	6.2	4.1	2.4	1.9	Module 2.7.1.2
					Mean	53.4	71.5	82.0	89.8	93.0	94.6	
					Range	(b)(4)						
					%CV	8.5	8.6	7.0	5.5	3.9	3.0	

(b)(4)

4.3.1.2.3 Dissolution Data - Sacubitril/Valsartan Tablets, 49 mg/51 mg [Reference product (Lot: FX000018)] vs. Test product (Batch No.: ME80344)] - Sacubitril

Dissolution Conditions		Apparatus:		(b)(4)								
		Speed of Rotation:	Medium:									
Firm's Proposed Specifications		Volume:		(b)(4)								
		Temperature:										
Dissolution Testing Site (Name, Address)		(b)(4)										
Study Ref No.	Testing Date	Product ID\Batch No. (Reference - Exp. Dt.) (Test - Mfg Dt.)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes)				Study Report Location			
					10	15	20	30		45	60	
Study Report	January 04, 2019	Entresto™ Sacubitril/valsartan tablets, 49 mg/51 mg Batch Number: FX000018 Expiry date: May, 2020^ Distributed by: Novartis pharmaceuticals corp, East Hanover, NJ07936	49 mg/51 mg, Tablets	12	Mean	59.4	81.0	92.0	97.1	98.7	99.2	Module 2.7.1.2
					Range	(b)(4)						
Study Report	January 03, 2019	Sacubitril/Valsartan Tablets, 49 mg/51 mg Batch Number: ME80344 Mfg. date: Dec, 2018	49 mg/51 mg, Tablets	12	%CV	7.4	6.3	6.4	4.3	2.5	2.0	Module 2.7.1.2
					Mean	52.5	70.9	82.7	91.6	95.2	96.8	
					Range	(b)(4)						
					%CV	9.6	5.0	5.8	4.7	2.9	1.8	

(b)(4)

4.3.1.2.4 Dissolution Data - Sacubitril/Valsartan Tablets, 49 mg/51 mg [Reference product (Lot: FX000018)] vs. Test product (Batch No.: ME80344)] - Valsartan

Dissolution Conditions		Apparatus:		(b)(4)		
		Speed of Rotation:	(b)(4)			
Firm's Proposed Specifications		Medium:		(b)(4)		
		Volume:	(b)(4)			
Dissolution Testing Site (Name, Address)		Temperature:		(b)(4)		
		Temperature:	(b)(4)			
Study Ref No.	Testing Date	Product ID/Batch No. (Reference - Exp. Dt.) (Test - Mfg Dt.)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes)	Study Report Location
Study Report	January 04, 2019	Entresto™ Sacubitril/valsartan tablets, 49 mg/51 mg Batch Number: FX000018 Expiry date: May, 2020^ Distributed by: Novartis pharmaceuticals corp, East Hanover, NJ07936	49 mg/51 mg, Tablets	12	10	Module 2.7.1.2
					15	
					20	
					30	
					45	
					60	
				Mean	58.7	97.8
				Range	80.0	97.3
				%CV	7.3	1.9
				Mean	51.9	95.5
				Range	70.0	93.9
				%CV	9.6	1.7
					(b)(4)	

(b)(4)

4.3.1.2.5 Dissolution Data - Sacubitril/Valsartan Tablets, 49 mg/51 mg [Reference product (Lot: FX000018)] vs. Test product (Batch No.: ME80345)] - Sacubitril

Dissolution Conditions		Apparatus:		(b)(4)		Speed of Rotation:		(b)(4)		Medium:		Volume:		Temperature:			
Firm's Proposed Specifications		(b)(4)															
Dissolution Testing Site (Name, Address)		(b)(4)															
Study Ref No.	Testing Date	Product ID/Batch No. (Reference - Exp. Dt.) (Test - Mfg Dt.)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes)					Mean	Range	% CV	Mean	Range	% CV	Study Report Location	
Study Report	January 04, 2019	Entresto™ Sacubitril/valsartan tablets, 49 mg/51 mg Batch Number: FX000018 Expiry date: May, 2020^ Distributed by: Novartis pharmaceuticals corp, East Hanover, NJ07936	49 mg/51 mg, Tablets	12	10	15	20	30	45	60	59.4	81.0	92.0	97.1	98.7	99.2	Module 2.7.1.2
					(b)(4)					7.4	6.3	6.4	4.3	2.5	2.0		
Study Report	January 04, 2019	Sacubitril/Valsartan Tablets, 49 mg/51 mg Batch Number: ME80345 Mfg. date: Dec, 2018	49 mg/51 mg, Tablets	12	(b)(4)					45.9	65.1	79.1	92.3	95.0	95.8	Module 2.7.1.2	
					(b)(4)					17.4	12.6	10.4	6.5	2.9	2.0		

(b)(4)

4.3.1.2.6 Dissolution Data - Sacubitril/Valsartan Tablets, 49 mg/51 mg [Reference product (Lot: FX000018)] vs. Test product (Batch No.: ME80345)] - Valsartan

Dissolution Conditions		Apparatus:		Collection Times (minutes)				Study Report Location				
		(b)(4)										
Speed of Rotation:		(b)(4)				Study Report Location						
Medium:		(b)(4)					Study Report Location					
Volume:		(b)(4)				Study Report Location						
Temperature:		(b)(4)					Study Report Location					
Firm's Proposed Specifications												
Dissolution Testing Site (Name, Address)												
(b)(4)												
Study Ref No.	Testing Date	Product ID/Batch No. (Reference - Exp. Dt.) (Test - Mfg Dt.)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes)				Study Report Location			
Study Report	January 04, 2019	Entresto™ Sacubitril/valsartan tablets, 49 mg/51 mg Batch Number: FX000018 Expiry date: May, 2020^ Distributed by: Novartis pharmaceuticals corp, East Hanover, NJ07936	49 mg/51 mg, Tablets	12	Mean	58.7	80.0	90.9	95.9	97.3	97.8	Module 2.7.1.2
					Range	(b)(4)						
Study Report	January 04, 2019	Sacubitril/Valsartan Tablets, 49 mg/51 mg Batch Number: ME80345 Mfg. date: Dec. 2018	49 mg/51 mg, Tablets	12	%CV	7.3	6.2	6.2	4.1	2.4	1.9	Module 2.7.1.2
					Mean	45.3	64.1	77.7	90.7	93.3	94.1	
					Range	(b)(4)						
					%CV	17.1	12.5	10.3	6.4	2.8	1.9	
(b)(4)												

4.3.1.3 Dissolution Data – 97 mg/103 mg Strength

4.3.1.3.1 Dissolution Data - Sacubitril/Valsartan Tablets, 97 mg/103 mg [Reference product (Lot: FX000024)] vs. Test product (Batch No.: ME80346) - **Sacubitril**

Dissolution Conditions		Apparatus:		Speed of Rotation:		Medium:		Volume:		Temperature:		
		(b)(4)										
Firm's Proposed Specifications		(b)(4)										
Dissolution Testing Site (Name, Address)		(b)(4)										
Study Ref No.	Testing Date	Product ID/Batch No. (Reference - Exp. Dt.) (Test - Mfg Dt.)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes)						Study Report Location	
Study Report	January 04, 2019	Entresto™ Sacubitril/Valsartan tablets, 97 mg/103 mg Batch Number: FX000024 Expiry date: May, 2020 Distributed by: Novartis pharmaceuticals corp, East Hanover, NJ07936	97 mg/103 mg, Tablets	12	Mean	44.7	63.1	77.7	91.3	95.7	96.6	Module 2.7.1.2
					Range	(b)(4)						
Study Report	January 03, 2019	Sacubitril/Valsartan Tablets, 97 mg/103 mg Batch Number: ME80346 Mfg. date: Dec, 2018	97 mg/103 mg, Tablets	12	%CV	11.5	8.3	7.2	4.0	1.4	1.2	Module 2.7.1.2
					Mean	41.1	61.1	77.5	93.0	97.2	98.2	
				Range		(b)(4)						
				%CV		20.1	15.0	11.0	5.0	2.5	2.0	

4.3.1.3.2 Dissolution Data - Sacubitril/Valsartan Tablets, 97 mg/103 mg [Reference product (Lot: FX000024)] vs. Test product (Batch No.: ME80346)] - Valsartan

Dissolution Conditions		Apparatus:		Speed of Rotation:		Medium:		Volume:		Temperature:		
				(b)(4)		(b)(4)						
Firm's Proposed Specifications		(b)(4)										
Dissolution Testing Site (Name, Address)		(b)(4)										
Study Ref No.	Testing Date	Product ID/Batch No. (Reference - Exp. Dt.) (Test - Mfg Dt.)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes)					Study Report Location		
					10	15	20	30	45	60		
		Entresto™ Sacubitril/valsartan tablets, 97 mg/103 mg Batch Number: FX000024 Expiry date: May, 2020 Distributed by: Novartis pharmaceuticals corp, East Hanover, NJ07936	97 mg/103 mg, Tablets	12	Mean	44.3	62.4	76.7	90.2	94.3	95.2	
Study Report	January 04, 2019				Range	(b)(4)						
					%CV	11.3	8.2	7.1	3.8	1.3	1.2	Module 2.7.1.2
					Mean	40.7	60.3	76.4	91.7	95.9	96.9	
Study Report	January 03, 2019	Sacubitril/Valsartan Tablets, 97 mg/103 mg Batch Number: ME80346 Mfg. date: Dec. 2018	97 mg/103 mg, Tablets	12	Range	(b)(4)						
					%CV	19.7	14.8	10.9	4.9	2.5	1.9	

4.3.1.3.3 Dissolution Data - Sacubitril/Valsartan Tablets, 97 mg/103 mg [Reference product (Lot: FX000024)] vs. Test product (Batch No.: ME80347)] - Sacubitril

Dissolution Conditions		Apparatus:		(b)(4)								
		Speed of Rotation:	Medium:									
Firm's Proposed Specifications		Volume:		(b)(4)								
		Temperature:										
Dissolution Testing Site (Name, Address)		(b)(4)										
Study Ref No.	Testing Date	Product ID/Batch No. (Reference - Exp. Dt.) (Test - Mfg Dt.)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes)			Study Report Location				
Study Report	January 04, 2019	Entresto™ Sacubitril/valsartan tablets, 97 mg/103 mg Batch Number: FX000024 Expiry date: May, 2020 Distributed by: Novartis pharmaceuticals corp, East Hanover, NJ07936	97 mg/103 mg, Tablets	12	Mean	44.7	63.1	77.7	91.3	95.7	96.6	Module 2.7.1.2
					Range	(b)(4)						
Study Report	January 03, 2019	Sacubitril/Valsartan Tablets, 97 mg/103 mg Batch Number: ME80347 Mfg. date: Dec. 2018	97 mg/103 mg, Tablets	12	%CV	11.5	8.3	7.2	4.0	1.4	1.2	Module 2.7.1.2
					Range	(b)(4)						
					%CV	10.5	5.9	4.5	3.2	2.2	1.8	

4.3.1.3.4 Dissolution Data – Sacubitril/Valsartan Tablets, 97 mg/103 mg [Reference product (Lot: FX000024)] vs. Test product (Batch No.: ME80347)] - Valsartan

Dissolution Conditions		Apparatus:		(b)(4)		Speed of Rotation:		(b)(4)		Medium:		Volume:		Temperature:	
Firm's Proposed Specifications		(b)(4)													
Dissolution Testing Site (Name, Address)		(b)(4)													
Study Ref No.	Testing Date	Product ID\Batch No. (Reference - Exp. Dt.) (Test - Mfg Dt.)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes)						Study Report Location				
					10	15	20	30	45	60					
Study Report	January 04, 2019	Entresto™ Sacubitril/valsartan tablets, 97 mg/103 mg Batch Number: FX000024 Expiry date: May, 2020 Distributed by: Novartis pharmaceuticals corp, East Hanover, NJ07936	97 mg/103 mg, Tablets	12	Mean	44.3	62.4	76.7	90.2	94.3	95.2	Module 2.7.1.2			
					Range	(b)(4)									
Study Report	January 03, 2019	Sacubitril/Valsartan Tablets, 97 mg/103 mg Batch Number: ME80347 Mfg. date: Dec, 2018	97 mg/103 mg, Tablets	12	%CV	11.3	8.2	7.1	3.8	1.3	1.2	Module 2.7.1.2			
					Mean	44.3	65.7	81.0	92.8	95.6	96.4				
					Range	(b)(4)									
					%CV	10.4	5.9	4.5	3.2	2.2	1.7				

4.3.1.3.5 Dissolution Data – Sacubitril/Valsartan Tablets, 97 mg/103 mg [Reference product (Lot: FX000024)] vs. Test product (Batch No.: ME80348)] - Sacubitril

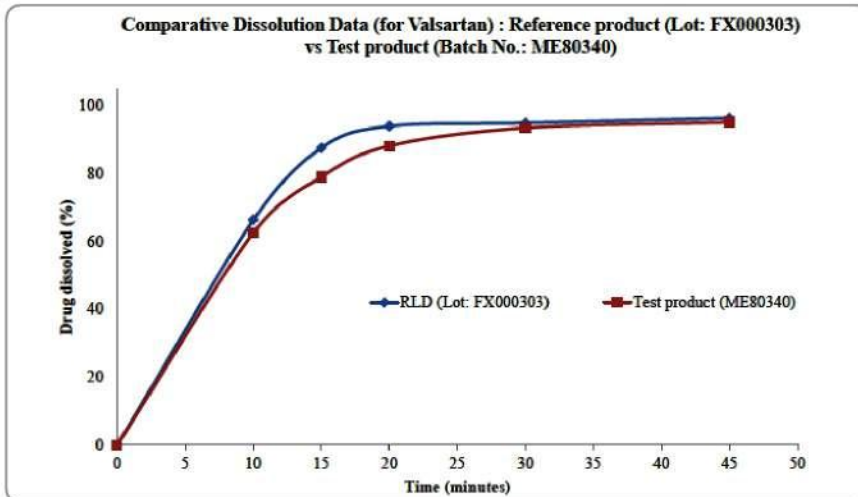
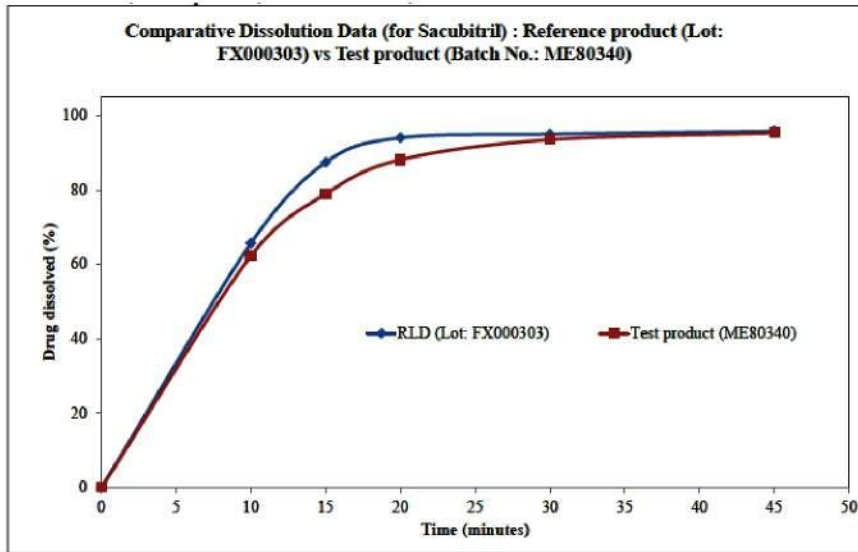
Dissolution Conditions		Apparatus:		Speed of Rotation:		Medium:		Volume:		Temperature:		
		(b)(4)										
Firm's Proposed Specifications		(b)(4)										
Dissolution Testing Site (Name, Address)		(b)(4)										
Study Ref No.	Testing Date	Product ID\Batch No. (Reference - Exp. Dt.) (Test - Mfg Dt.)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes)						Study Report Location	
Study Report	January 04, 2019	Entresto™ Sacubitril/valsartan tablets, 97 mg/103 mg Batch Number: FX000024 Expiry date: May, 2020 Distributed by: Novartis pharmaceuticals corp, East Hanover, NJ07936	97 mg/103 mg, Tablets	12	Mean	44.7	63.1	77.7	91.3	95.7	96.6	Module 2.7.1.2
					Range	(b)(4)						
Study Report	January 03, 2019	Sacubitril/Valsartan Tablets, 97 mg/103 mg Batch Number: ME80348 Mfg. date: Dec. 2018	97 mg/103 mg, Tablets	12	%CV	11.5	8.3	7.2	4.0	1.4	1.2	Module 2.7.1.2
					Range	(b)(4)						
					%CV	14.5	10.7	7.5	3.3	2.3	1.6	

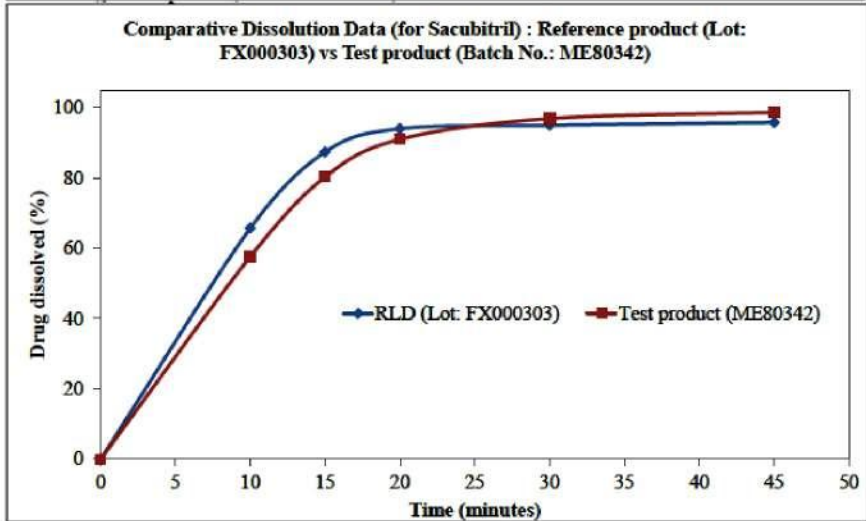
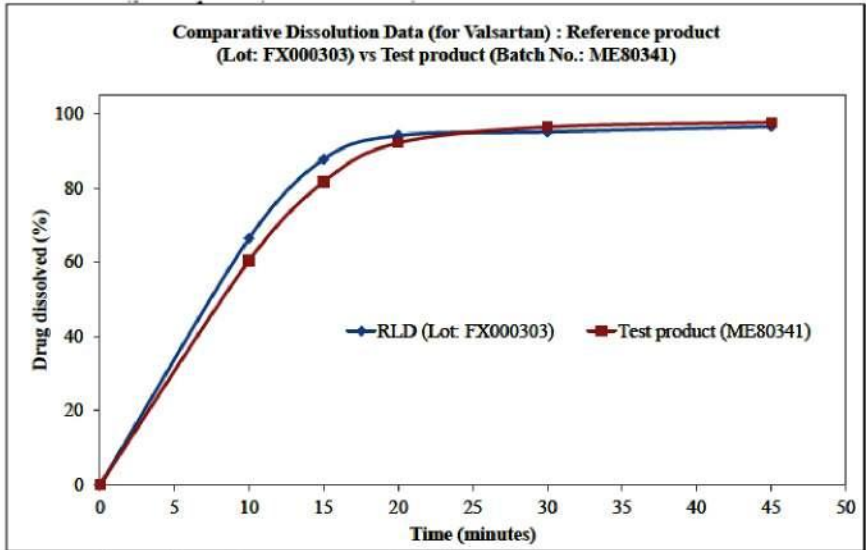
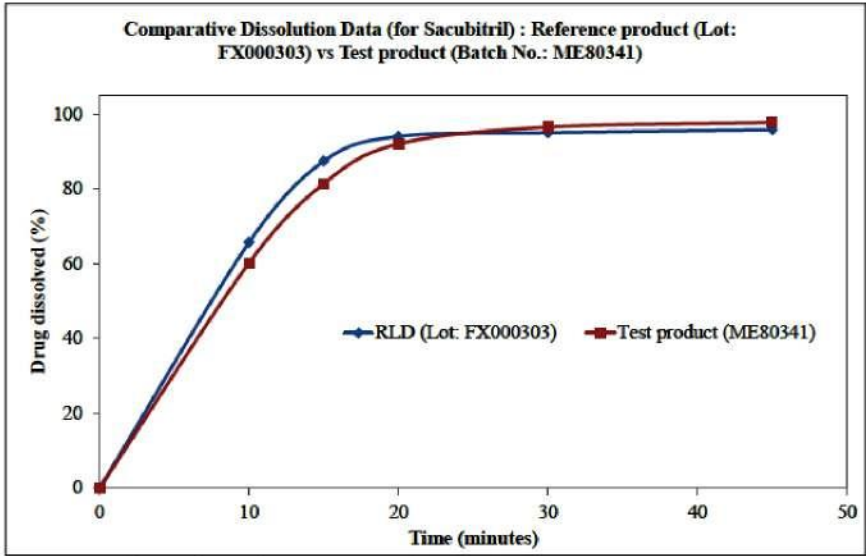
4.3.1.3.6 Dissolution Data – Sacubitril/Valsartan Tablets, 97 mg/103 mg [Reference product (Lot: FX000024)] vs. Test product (Batch No.: ME80348)] - Valsartan

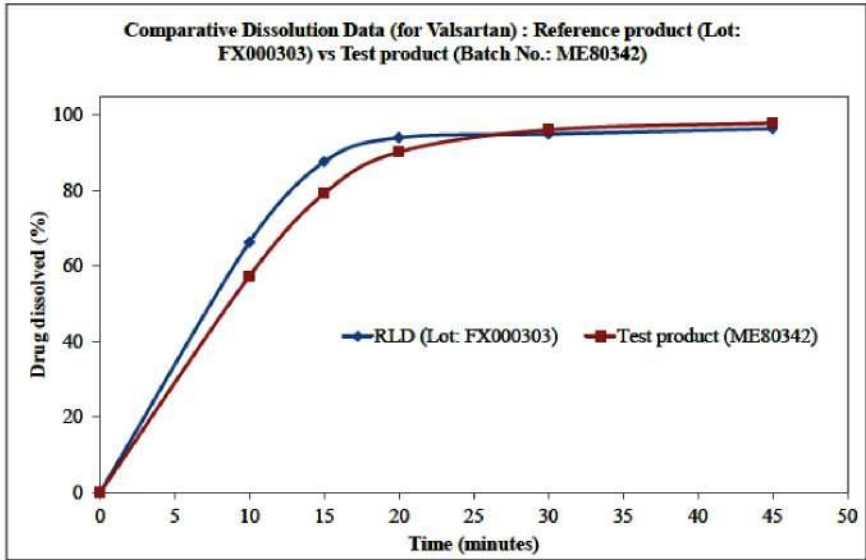
Dissolution Conditions		Apparatus:		Speed of Rotation:		Medium:		Volume:		Temperature:		
		(b)(4)										
Firm's Proposed Specifications		(b)(4)										
Dissolution Testing Site (Name, Address)		(b)(4)										
Study Ref No.	Testing Date	Product ID\Batch No. (Reference - Exp. Dt.) (Test - Mfg Dt.)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes)						Study Report Location	
Study Report	January 04, 2019	Entresto™ Sacubitril/valsartan tablets, 97 mg/103 mg Batch Number: FX000024 Expiry date: May, 2020 Distributed by: Novartis pharmaceuticals corp, East Hanover, NJ07936	97 mg/103 mg, Tablets	12	Mean	44.3	62.4	76.7	90.2	94.3	95.2	Module 2.7.1.2
					Range	(b)(4)						
Study Report	January 03, 2019	Sacubitril/Valsartan Tablets, 97 mg/103 mg Batch Number: ME80348 Mfg. date: Dec, 2018	97 mg/103 mg, Tablets	12	%CV	11.3	8.2	7.1	3.8	1.3	1.2	Module 2.7.1.2
					Range	(b)(4)						
					%CV	14.1	10.6	7.4	3.2	2.2	1.6	

4.3.2 Dissolution Profiles

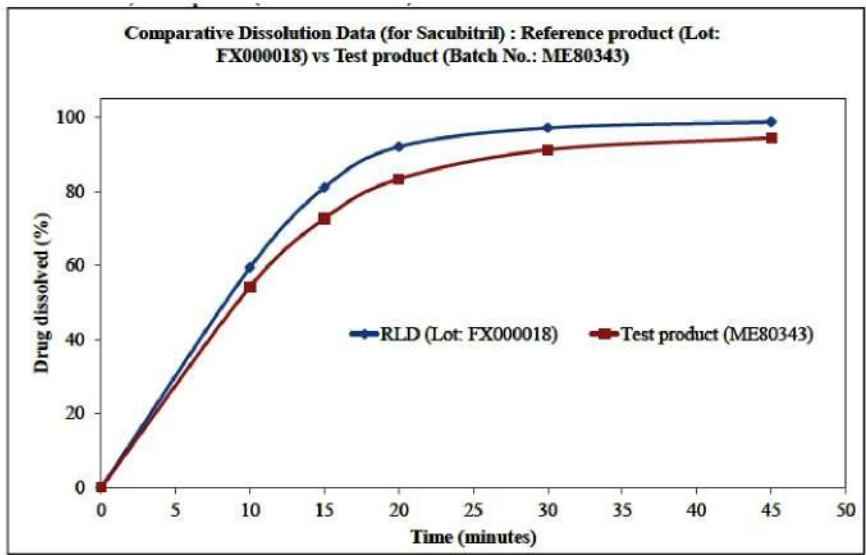
4.3.2.1 Dissolution Profiles – 24 mg/26 mg Strength

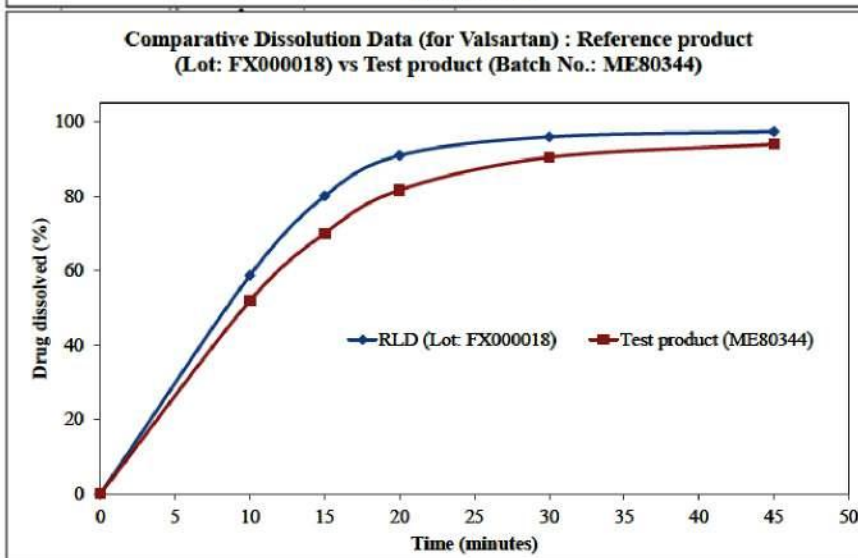
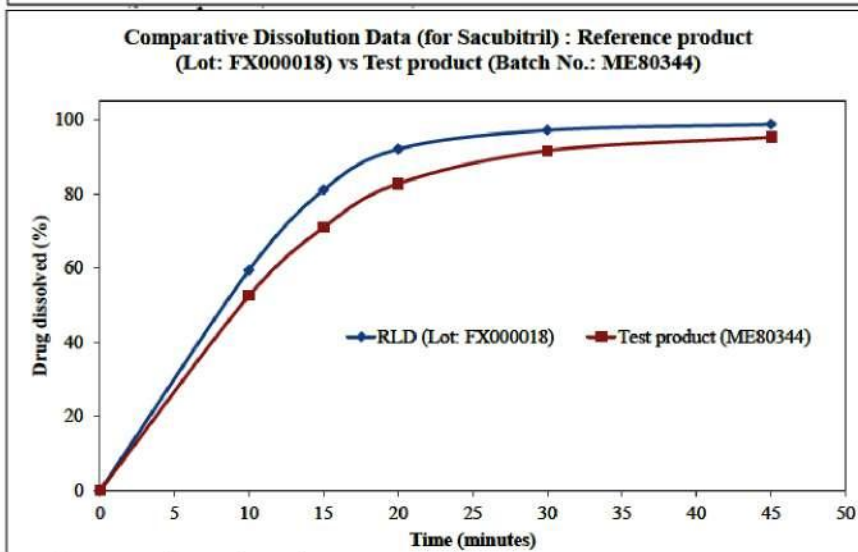
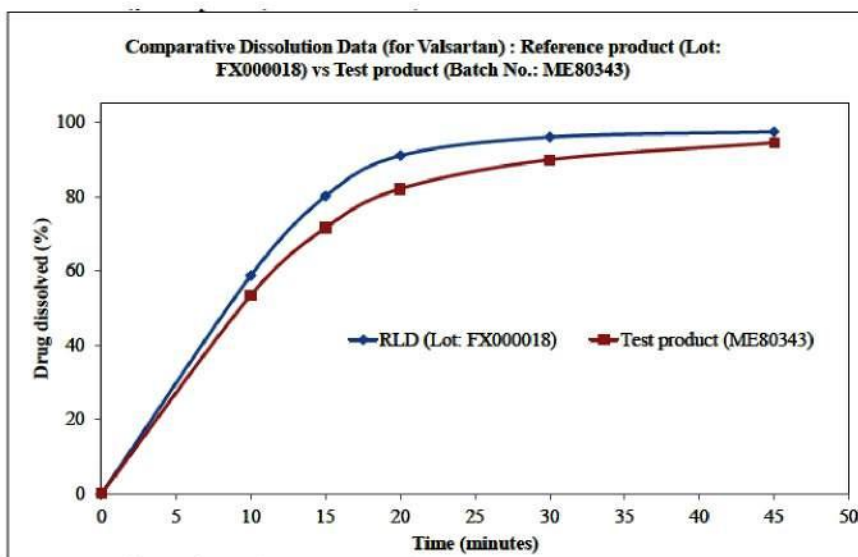


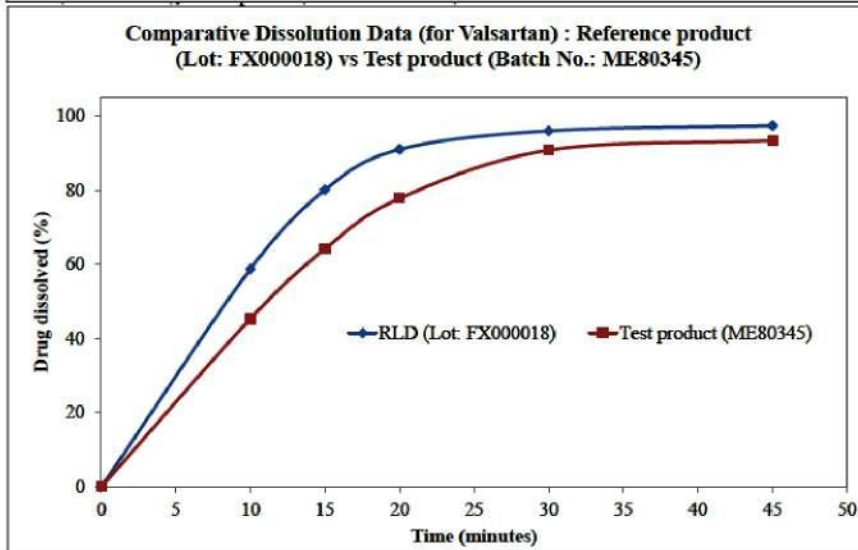
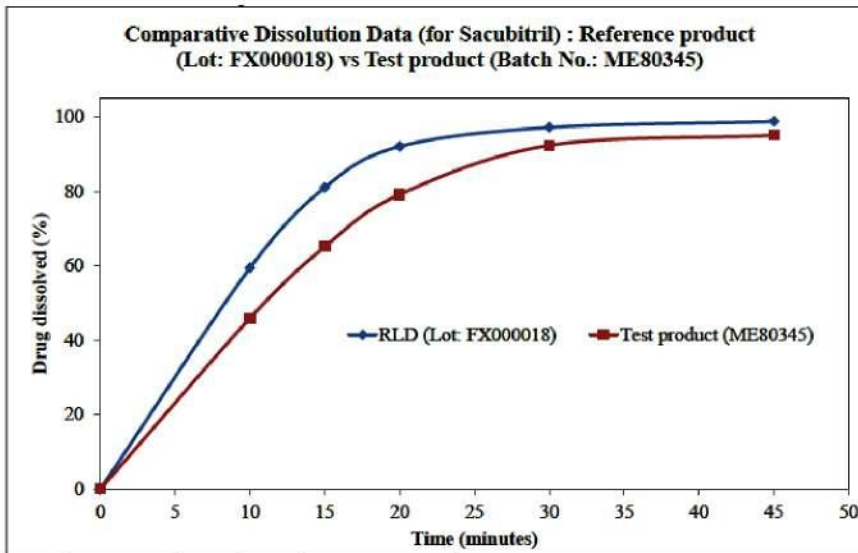




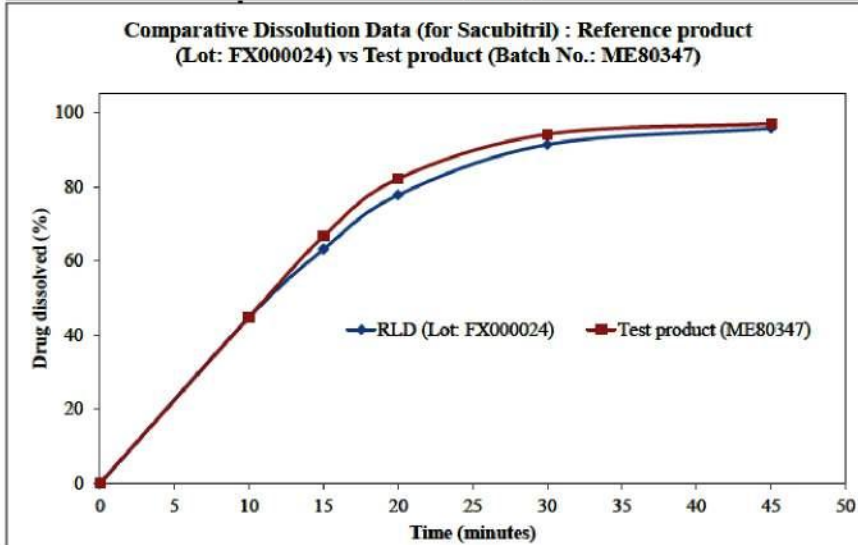
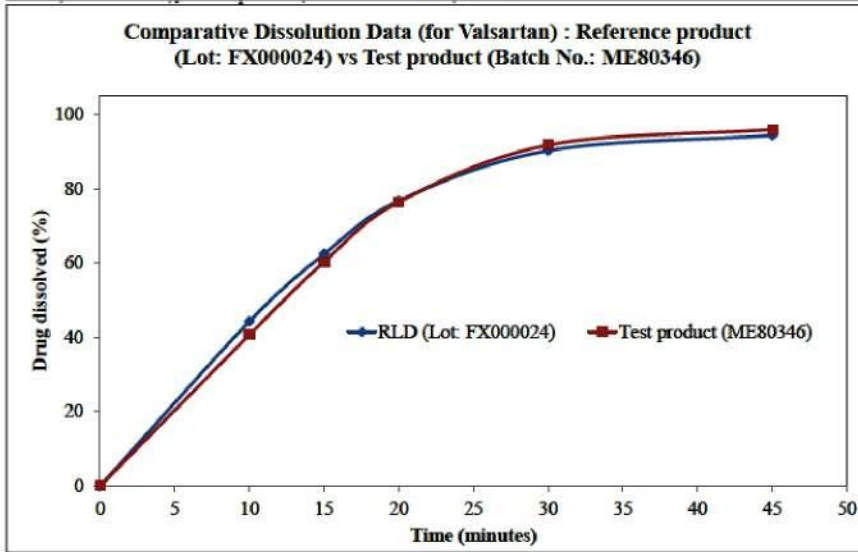
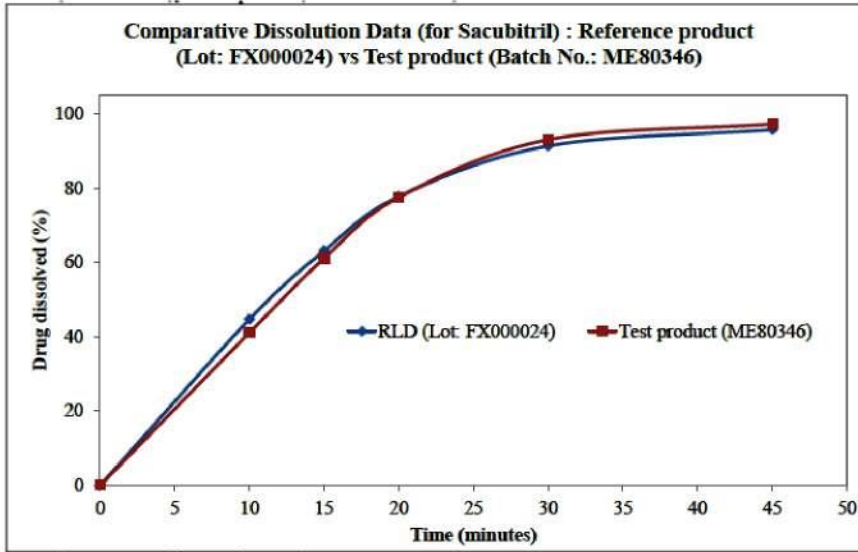
4.3.2.2 Dissolution Profiles – 49 mg/51 mg Strength

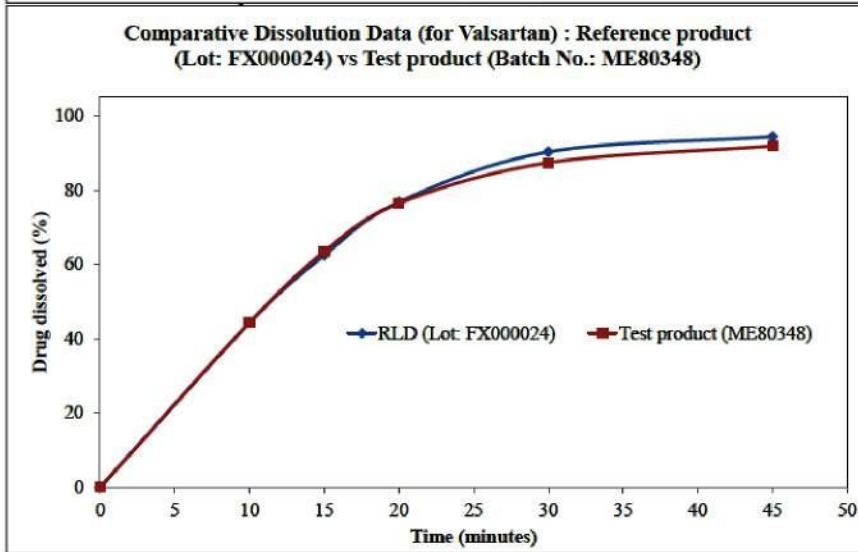
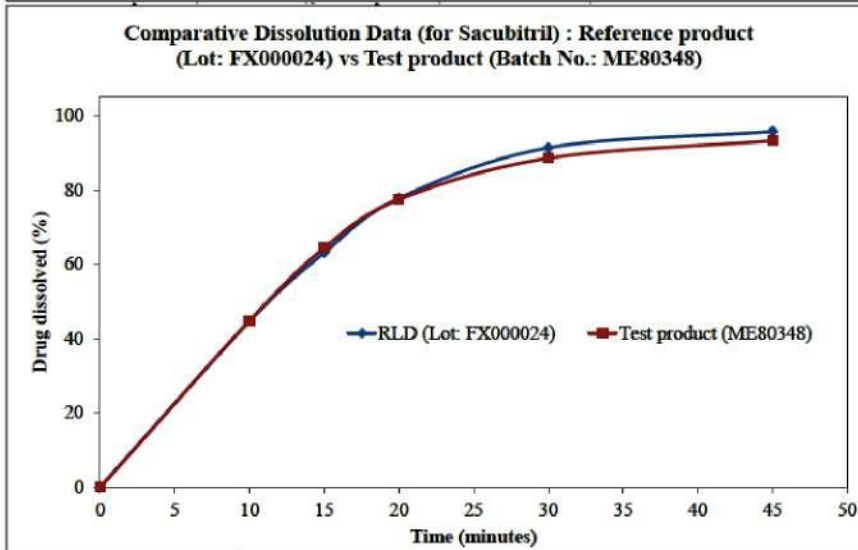
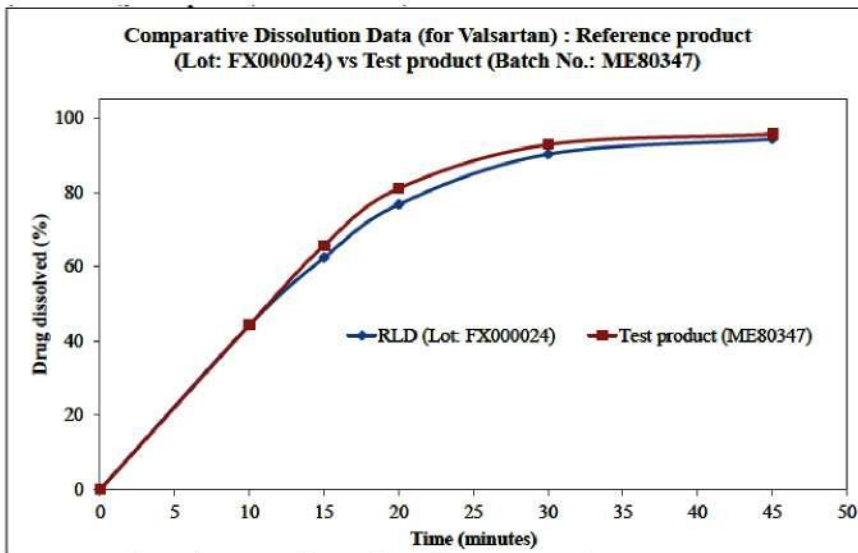






4.3.2.3 Dissolution Profiles – 97 mg/103 mg Strength





4.3.3 F2 Metric

F2 metric calculated?	☐ Yes ☒ No
If no, reason why F2 not calculated	Rapid dissolving

Please comment on whether dissolution data are adequate to support requests submitted under 21 CFR 320.22(d)(2) or 320.24(b)(6).	Incomplete

Overall Comments: Incomplete

- The applicant provided comparative *in vitro* dissolution data for 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg strengths between the test and reference products. The applicant's dissolution method (b)(4) is consistent with the previous FDA-recommended dissolution method. It is noted that the FDA's dissolution database was updated on 10/24/2019 to propose testing sacubitril and valsartan tablets using USP Apparatus I (basket) at 75 rpm instead of (b)(4).

The dissolution-only assessment has been completed, and the dissolution method is considered inadequate.⁴ The biopharmaceutics assessor states that the proposed dissolution method "is not acceptable at this stage because (b)(4)

(b)(4)
The

biopharmaceutics assessor stated in the Information Request deficiency letter that the data/information provided in the submission are not adequate to demonstrate the suitability /discriminating ability of the proposed dissolution method for the test product, they also asked for explanation for root cause of the incomplete dissolution and observed high variability, and asked for dissolution data using the current FDA-recommended dissolution method.

- For each of the 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg strengths, the QC dissolution test was conducted on 1 unexpired reference batch and 3 test batches. For the 97 mg/103 mg strength, the reference batch (batch #FX000024) and 1 of the 3 test batches (test batch #ME80346) were the same batches used in the fasting and fed studies for the 97 mg/103 mg strength. For the 24 mg/26 mg strength, the reference batch (batch #FX000303) and 1 of the 3 test batches (test batch #ME80340) were the same batches used in the fasting study for the 24 mg/26 mg strength.
- Based on the mean dissolution data, both the test and reference products showed (b)(4) dissolution profiles (b)(4)

The dissolution data are **inadequate** to support biowaiver for the 24 mg/26 mg and 49 mg/51 mg strengths of the test product due to inadequate dissolution method as stated in the biopharmaceutics assessment.

4.4 Attachments

4.4.1 Additional Studies

		☒ Yes ☐ No		
Are there any additional studies? (e.g. pilot, failed) If yes, please provide the location of report (complete/summary).	Additional fasting study for the 24 mg/26 mg strength (study #BA18086667) Summary in 7/8/2019 submission, Module 2.7.1\2.7.1 Summary of Biopharmaceutic Studies... Complete reports in Module 5.3.1.2. ba18086667 ... and Module 5.3.1.4. ba18086667	Pilot fasting study for the 97 mg/103 mg strength (study #BA17861001-01) Summary in 7/8/2019 submission, Module 2.7.1\2.7.1 Summary of Biopharmaceutic Studies...	Pilot fed study for the 97 mg/103 mg strength (study #BA17861002-01) Summary in 7/8/2019 submission, Module 2.7.1\2.7.1 Summary of Biopharmaceutic Studies...	Pilot fasting and fed studies for the 97 mg/103 mg strength (study # no specified) The applicant did not provide summary tables or study report, as they stated that the formulation of the test batch (#97+103-F030A) used in these pilot studies is not considered the same as the one used in pivotal PK studies.⁵
Number of Subjects	38	15	15	Not specified
Are the test formulations in the pilot/failed studies and pivotal studies similar³⁸?	☒ Yes ☐ No	☒ Yes ☐ No	☒ Yes ☐ No	☐ Yes ☒ No [as stated by the applicant ⁵ , no formulation table is provided for the test batch (97+103-F030A) used]
What was the objective of pilot/failed study?	To compare and evaluate the oral bioavailability of the test with that of reference product for the 24 mg/26 mg strength under fasting condition, as the applicant's f2 value is less than 50 for 24 mg/26 mg strength in comparison with 97 mg/103 mg strength for both sacubitril and valsartan.³	To understand the potential clinical relevance of formulation on in vivo performance	To understand the potential clinical relevance of formulation on in vivo performance	Not specified

³⁸ [Submission of Summary Bioequivalence Data for Abbreviated New Drug Applications](#)

Please comment on reason(s) of failure.	N/A (the study passed based on the applicant's results) ☐ Yes ☒ No	Underpowered ☐ Yes ☒ No	N/A (no study information is submitted since the applicant stated that the formulation is not considered the same as compared to the bio-batch)
Any serious adverse events or deaths reported?		☐ Yes ☒ No	No AE information is provided. However, given that these pilot studies did not use the same test formulation as compared to the bio-batch as stated by the applicant, and the 2 pivotal studies as well as the 3 other additional studies (study #s BA18086667, BA17861001-01 and BA17861002-01) did not report SAEs or deaths, and only reported limited number of AEs, the risk of SAE and death in these pilot studies using test batch #97+103-F030A is low. Therefore, the assessor will not ask the applicant to specify if any SAE or deaths were reported for these pilot studies.

4.4.1.1 Summary Tables for Fasting Study #BA18086667 for the 24 mg/26 mg Strength

Assessor's Note: The applicant stated that in the dissolution study using the QC dissolution method, the applicant's f2 value is less than 50 for 24 mg/26 mg strength in comparison with 97 mg/103 mg strength for both sacubitril and valsartan.³ However, as mentioned in Section 4.3.3, it is noted that the test and reference products showed [] dissolution profiles based on mean dissolution data, hence no f2 calculation was conducted by the assessor. Since there is a potential that this [] dissolving observation could be used to support waiver of the 24 mg/26 mg and 49 mg/51 mg strengths, if the applicant could adequately address the biopharmaceutics assessor's concern on the dissolution method (currently, the biopharmaceutics assessor considers the applicant's dissolution method inadequate⁴). Therefore, this fasting study for the 24 mg/26 mg strength is not extensively assessed and is listed below for information only in the current assessment. In the future, if the applicant could not resolve the dissolution method issue to support biowaiver, then this fasting study may be assessed extensively.

Table 1: Submission Summary

Drug Product Name	Sacubitril/Valsartan Tablets
Strength(s)	97 mg/103 mg
Applicant Name	Zydus Pharmaceuticals (USA), Inc.
Address	73-B, Route 31 North, Pennington, NJ 08534
Point of Contact Name	Srinivas Gurram (Srini)
Address	Zydus Pharmaceuticals (USA), Inc. 73-B, Route 31 North, Pennington, NJ 08534
Telephone Number	609-730-1900 (Ext: 110)
Fax Number	609-730-1999

Table 2 (A): Summary of Bioavailability Studies – (Fasting Study # BA18086667) - Sacubitril

Study Ref. No.	Study Objective	Study Design	Treatment (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (range))	(Mean Parameters ± SD) (%CV)						Study Report Location
					Cmax (ng/mL)	Tmax (hr)	AUCt (ng*hr/mL)	AUCi (ng*hr/mL)	tHalf (hr)	Kel (1/hr)	
Study # BA18086667	- To compare and evaluate the oral bioavailability of Sacubitril and Valsartan Tablets 24 mg/26 mg with that of 'ENTRESTO™' (Sacubitril and Valsartan) Tablets 24 mg/26 mg in healthy, adult, human subjects under fasting conditions. - To monitor the safety of the subjects.	An open label, randomized, four-period, two-treatment, two-sequence, fully replicate, single-dose, crossover, balanced, fasting, study design.	Test Product: Sacubitril/ Valsartan Tablets 24 mg /26 mg, 1 × (24 mg /26 mg), Oral, [Batch No.: ME80368 (Mother Batch # ME80340)] Reference Product: Entresto™ (Sacubitril/ Valsartan) Tablets 24 mg/26 mg, 1 × (24 mg /26 mg), Oral, [Lot No.: FX000303]	38 dosed, 30 completed study (30 males) Age: 34 (23-43) years Healthy male subjects.	517.117 ±257.215 (49.740)	0.500 (0.333-5.000)	556.037 ±167.641 (30.149)	561.857 ±167.557 (29.822)	0.819 ±0.200 (24.457)	0.892 ±0.208 (23.329)	Module 5.3.1.2 Page no. 01 to 142 of study report
					546.143 ±232.083 (42.495)	0.500 (0.333-2.667)	560.444 ±142.001 (25.337)	566.130 ±142.418 (25.156)	0.824 ±0.162 (19.618)	0.874 ±0.176 (20.166)	

Note: The mean age is calculated based on completed subjects. Tmax is presented as Median (Range).

Table 2 (B): Summary of Bioavailability Studies – (Fasting Study # BA18086667) - Valsartan

Study Ref. No.	Study Objective	Study Design	Treatment (Dose, Dosage Form, Route [Product ID])	Subjects (No. (M/F) Type Age: mean (range))	(Mean Parameters ± SD) (% CV)						Study Report Location
					Cmax (ng/mL)	Tmax (hr)	AUCt (ng*hr/mL)	AUCi (ng*hr/mL)	tHalf (hr)	Kel (1/hr)	
Study # BA18086667	- To compare and evaluate the oral bioavailability of Sacubitril and Valsartan Tablets 24 mg/26 mg with that of 'ENTRESTO™' (Sacubitril and Valsartan) Tablets 24 mg/26 mg in healthy, adult, human subjects under fasting conditions. - To monitor the safety of the subjects.	An open label, randomized, four-period, two-treatment, two-sequence, fully replicate, single-dose, crossover, balanced, fasting, study design.	Test Product: Sacubitril/ Valsartan Tablets 24 mg /26 mg, 1 x (24 mg / 26 mg), Oral, [Batch No.: ME80368 (Mother Batch # ME80340)] Reference Product: Entresto™ (Sacubitril/ Valsartan) Tablets 24 mg/26 mg, 1 x (24 mg /26 mg), Oral, [Lot No.: FX000303]	38 dosed, 30 completed study (30 males) Age: 34 (23-43) years Healthy male subjects.	1276.107 ±432.930 (33.926)	1.500 (1.000-4.000)	8261.810 ±3312.589 (40.095)	8409.597 ±3397.863 (40.405)	7.808 ±3.167 (40.557)	0.103 ±0.040 (39.158)	Module 5.3.1.2 Page no. 01 to 142 of study report

Table 3(A1): Statistical Summary of the Comparative Bioavailability Data for Unscaled Average BE studies (Fasting Study # BA18086667) – Sacubitril

Reference Scaled Average Bioequivalence Approach Used ☒ Yes ☐ No						
If No, then complete Table 3A1 only						
If Yes, then complete Tables 3A1 and 3B1						
Sacubitril / Valsartan Tablets (No of subjects completed= 30) 1 × (24 mg / 26 mg)						
Least Square Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fasting Bioequivalence Study (BA18086667)						
Parameter	Test	N	RLD	N	Ratio	90% CI
AUCt	525.230	60	546.226	60	96.16%	(89.15%; 103.72%)
AUCi	531.520	60	551.927	60	96.30%	(89.38%; 103.76%)
Cmax	452.198	60	498.947	60	90.63%	NA

Notes:-

- NA = Not Applicable; the within subject standard deviation of reference product (S_{WR}) of Cmax was greater than 0.294. Hence, Scaled Average Bioequivalence approach was used to assess bioequivalence for Cmax parameter.
- The within subject standard deviation of reference product (S_{WR}) of AUCt and AUCi were less than 0.294. Hence, Average Bioequivalence approach was used to assess bioequivalence for AUCt and AUCi parameters.

Table 3(A2): Statistical Summary of the Comparative Bioavailability Data for Unscaled Average BE studies (Fasting Study # BA18086667) – Valsartan

Reference Scaled Average Bioequivalence Approach Used ☒ Yes ☐ No						
If No, then complete Table 3A2 only						
If Yes, then complete Tables 3A2 and 3B2						
Sacubitril / Valsartan Tablets (No of subjects completed= 30) 1 × (24 mg / 26 mg)						
Least Square Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fasting Bioequivalence Study (BA18086667)						
Parameter	Test	N	RLD	N	Ratio	90% CI
AUCt	7486.787	60	8139.975	60	91.98%	(82.96%; 101.98%)
AUCi	7618.291	60	8279.239	60	92.02%	(83.15%; 101.83%)
Cmax	1188.430	60	1296.311	60	91.68%	NA

Notes:-

- NA = Not Applicable; the within subject standard deviation of reference product (S_{WR}) of Cmax was greater than 0.294. Hence, Scaled Average Bioequivalence approach was used to assess bioequivalence for Cmax parameter.
- The within subject standard deviation of reference product (S_{WR}) of AUCt and AUCi were less than 0.294. Hence, Average Bioequivalence approach was used to assess bioequivalence for AUCt and AUCi parameters.

Table 3(B1): Statistical Summary of the Comparative Bioavailability Data for Reference-Scaled Average BE Studies – (Fasting Study # BA18086667) - Sacubitril

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	Outcome
LAUCt	96.16%*	89.15%	103.72%	0.0064	0.080	NA	Average Bioequivalence	Bioequivalent
LAUCi	96.30%*	89.38%	103.76%	0.0063	0.079	NA	Average Bioequivalence	Bioequivalent
LCmax	0.91^	NA	NA	0.1511	0.389	-0.0598	Scaled Average Bioequivalence	Bioequivalent

Notes:-

- NA = Not Applicable
- *=T/R ratio presented in percentage (%) of Unscaled average bioequivalence method.
- ^=point estimate of Scaled average bioequivalence method as per protocol.

Table 3(B2): Statistical Summary of the Comparative Bioavailability Data for Reference-Scaled Average BE Studies – (Fasting Study # BA18086667) – Valsartan

Parameter	T/R Ratio	Lower 90% CI	Upper90% CI	s2wr	sWR	Criteria Bound	Method Used	Outcome
LAUCt	91.98%*	82.96%	101.98%	0.0740	0.272	NA	Average Bioequivalence	Bioequivalent
LAUCi	92.02%*	83.15%	101.83%	0.0661	0.257	NA	Average Bioequivalence	Bioequivalent
LCmax	0.92^	NA	NA	0.1011	0.318	-0.0314	Scaled Average Bioequivalence	Bioequivalent

- NA = Not Applicable
- *=T/R ratio presented in percentage (%) of Unscaled average bioequivalence method.
- ^=point estimate of Scaled average bioequivalence method as per protocol.

Table 4 (A): Bioanalytical Method Validation – (Fasting Study # BA18086667) Sacubitril

Information Requested	Data
Bioanalytical method validation report location	Module 5/ Section 5.3.1.4/ Attachment 6(i) / Method Validation Report / Page 01 to 148
Analyte	Sacubitril
Internal standard (IS)	Sacubitril D4
Method description	Solid phase extraction with LC/MS/MS method
Limit of quantitation	2.500 ng/mL
Average recovery of drug (%)	93.6%
Average recovery of IS (%)	89.3%
Standard curve concentrations (ng/mL)	2.500, 5.000, 15.00, 45.00, 100.0, 300.0, 600.0, 900.0, 1200 and 1500

QC concentrations (ng/mL)	7.500, 90.00, 525.0 and 1125
QC Intraday precision range (%)	0.8% to 3.0% (Intra-run)
QC Intraday accuracy range (%)	93.2% to 105% (Intra-run)
QC Interday precision range (%)	1.8% to 3.0% (Inter-run)
QC Interday accuracy range (%)	94.2% to 103% (Inter-run)
Bench-top stability (hrs)	25 hours at room temperature (15°C to 25°C) (For Sacubitril) 24 hours at room temperature (15°C to 25°C) [For Sacubitril fortified with Metabolite Sacubitrilat (LBQ657) and 4-Hydroxy Valsartan (1500/3000 ng/mL)]
Stock stability (days)	15 days for drug and for internal standard-1 at refrigerator temperature (5°C±3°C)
Processed stability (hrs)	104 hours at room temperature (15°C to 25°C) and 103 hours at refrigerator temperature (5°C±3°C) (For Sacubitril) 108 hours at room temperature (15°C to 25°C) and at refrigerator temperature (5°C±3°C) [For Sacubitril fortified with Metabolite Sacubitrilat (LBQ657) and 4-Hydroxy Valsartan (1500/3000 ng/mL)]
Freeze-thaw stability (cycles)	6 freeze thaw cycles (For Sacubitril) 6 freeze thaw cycles [For Sacubitril fortified with Metabolite Sacubitrilat (LBQ657) and 4-Hydroxy Valsartan (1500/3000 ng/mL)]
Long-term storage stability (days)	41 Days at -20°C ± 7°C temperature (For Sacubitril) 40 Days at -20°C ± 7°C temperature [For Sacubitril fortified with Metabolite Sacubitrilat (LBQ657) and 4-Hydroxy Valsartan (1500/3000 ng/mL)]
Dilution integrity	12000 ng/mL, diluted to 10 times 2250 ng/mL, diluted to 02 times
Selectivity	No significant interfering peak noted in blank plasma lots

**Table 4 (B): Bioanalytical Method Validation – (Fasting Study # BA18086667)
Valsartan**

Information Requested	Data
Bioanalytical method validation report location	Module 5/ Section 5.3.1.4/ Attachment 6(i) / Method Validation Report / Page 01 to 148
Analyte	Valsartan
Internal standard (IS)	Valsartan D9
Method description	Solid phase extraction with LC/MS/MS method
Limit of quantitation	5.000 ng/mL
Average recovery of drug (%)	94.4%

Average recovery of IS (%)	87.3%
Standard curve concentrations (ng/mL)	5.000, 10.00, 30.00, 90.00, 200.0, 600.0, 1200, 1800, 2400 and 3000
QC concentrations (ng/mL)	15.00, 180.0, 1050 and 2250
QC Intraday precision range (%)	1.6% to 3.5% (Intra-run)
QC Intraday accuracy range (%)	95.7% to 104% (Intra-run)
QC Interday precision range (%)	2.1% to 3.2% (Inter-run)
QC Interday accuracy range (%)	97.0% to 103% (Inter-run)
Bench-top stability (hrs)	25 hours at room temperature (15°C to 25°C) (For Valsartan) 24 hours at room temperature (15°C to 25°C) [For Valsartan fortified with Metabolite Sacubitrilat (LBQ657) and 4-Hydroxy Valsartan (1500/3000 ng/mL)]
Stock stability (days)	15 days for drug and for internal standard-2 at refrigerator temperature (5°C±3°C)
Processed stability (hrs)	104 hours at room temperature (15°C to 25°C) and 103 hours at refrigerator temperature (5°C±3°C) (For Valsartan) 108 hours at room temperature (15°C to 25°C) and at refrigerator temperature (5°C±3°C) [For Valsartan fortified with Metabolite Sacubitrilat (LBQ657) and 4-Hydroxy Valsartan (1500/3000 ng/mL)]
Freeze-thaw stability (cycles)	6 freeze thaw cycles (For Valsartan) 6 freeze thaw cycles [For Valsartan fortified with Metabolite Sacubitrilat (LBQ657) and 4-Hydroxy Valsartan (1500/3000 ng/mL)]
Long-term storage stability (days)	41 Days at -20°C ± 7°C temperature (For Valsartan) 40 Days at -20°C ± 7°C temperature [For Valsartan fortified with Metabolite Sacubitrilat (LBQ657) and 4-Hydroxy Valsartan (1500/3000 ng/mL)]
Dilution integrity	24000 ng/mL, diluted to 10 times 4500 ng/mL, diluted to 02 times
Selectivity	No significant interfering peak noted in blank plasma lots

Table 5 Summary of In Vitro Dissolution Studies

Please see Section 4.3.1

**Table 6: Formulation Data
Qualitative and Quantitative composition of Sacubitril/Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg**

Sr. No.	Name of Ingredient	Quantity per Unit (mg)		% w/w**		Function
		24 mg/26 mg	49 mg/51 mg	97 mg/103 mg	49 mg/51 mg	
	Sacubitril/Valsartan* [®]	(b)(4)		(b)(4)		Active ingredient
	Microcrystalline Cellulose NF	(b)(4)		(b)(4)		
	Low Substituted Hydroxy Propyl Cellulose NF	(b)(4)		(b)(4)		
	Colloidal Silicon Dioxide, NF	(b)(4)		(b)(4)		
	Sodium Stearyl Fumarate NF	(b)(4)		(b)(4)		
	Crospovidone NF	(b)(4)		(b)(4)		
Total (Film Coated Tablets)		105,450	210,900	402,000	100.00	100.00
						-

(b)(4)

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Table 7: Demographic Profile of Subjects Completing the Bioequivalence Study – (Fasting Study # BA18086667)

Study No. BA18086667			
		Treatment Groups	
		Test Product N = 30	Reference Product N = 30
Age (years)	Mean ± SD	34 ± 6	34 ± 6
	Range	23 - 43	23 - 43
Age Groups	< 18	0 (0.00%)	0 (0.00%)
	18 – 40	26 (86.67%)	26 (86.67%)
	41 – 64	4 (13.33%)	4 (13.33%)
	65 – 75	0 (0.00%)	0 (0.00%)
	> 75	0 (0.00%)	0 (0.00%)
Sex	Male	30 (100.00%)	30 (100.00%)
	Female	0 (0.00%)	0 (0.00%)
Race	Asian	30 (100.00%)	30 (100.00%)
	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 (Kg/m ²)	Mean ± SD	24.0 ± 3.2	24.0 ± 3.2
	Range	18.8 – 29.7	18.8 – 29.7
Tobacco Users/ Smokers	Yes	0 (0.00%)	0 (0.00%)
	No	30 (100.00%)	30 (100.00%)

Table 8: Incidence of Adverse Events in Individual Studies – (Fasting Study # BA18086667)

(1) Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Fasting Bioequivalence Study Study No. BA18086667	
	Test (T) (2) N= 34* (3) n (%)	Reference (R) (2) N= 36# (3) n (%)
General disorders and administration site conditions		
Pyrexia	0 (0.00%)	2 (5.56%)
Nervous system disorders		
Dizziness	1 (2.94%)	0 (0.00%)
Gastrointestinal disorders		
Vomiting	1 (2.94%)	0 (0.00%)

Total	1 (2.94%)	2 (5.56%)

(1) Med DRA Version 22.0

(2) N=Number of subjects dosed for each treatment

(3) n= Number of subjects reporting at least one incidence of respective adverse event; (%)=percentage of subjects reporting at least one incidence of respective adverse event.

*31 subjects were dosed twice with Test product in two different periods and 03 subjects were dosed with Test product only once in either of the periods.

31 subjects were dosed twice with Reference product in two different periods and 05 subjects were dosed with Reference product only once in either of the periods.

Table 9 (A): Reanalysis of Study Samples – (Fasting Study # BA18086667) - Sacubitril

Study No. BA18086667 Additional information in Module 5/Section 5.3.1.4/ Sample Analysis Report/ Page 63 of 141								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0.00	0.00	0	0	0.00	0.00
Low internal standard	2	0	0.12	0.00	2	0	0.12	0.00
Total	2	0	0.12	0.00	2	0	0.12	0.00

Note: Total number of samples assayed = 3274

Total number of samples assayed for Test Product (T) = 1602

Total number of samples assayed for Reference Product (R) = 1672

Table 9 (B): Reanalysis of Study Samples – (Fasting Study # BA18086667) - Valsartan

Study No. BA18086667 Additional information in Module 5/Section 5.3.1.4/ Sample Analysis Report/Page 63 of 141								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0.00	0.00	0	0	0.00	0.00
Low internal standard	2	0	0.12	0.00	2	0	0.12	0.00
Total	2	0	0.12	0.00	2	0	0.12	0.00

Note: Total number of samples assayed = 3274

Total number of samples assayed for Test Product (T) = 1602

Total number of samples assayed for Reference Product (R) = 1672

Table 10: Study Information – (Fasting Study # BA18086667) – Sacubitril and Valsartan

Study Number	BA18086667
Study Title	Single dose oral bioequivalence study of Sacubitril and Valsartan Tablets 24 mg/26 mg and ‘ENTRESTO™’ (Sacubitril and Valsartan) Tablets 24 mg/26 mg in healthy adult human subjects under fasting conditions.
Study Type	☒ In Vivo ☐ BE In Vitro ☐ BE Permeability ☐ Other
Submission Location: o Study Report o Validation Report o Bioanalytical Report	location, 5.3.1.2 location, 5.3.1.4 location, 5.3.1.4
Clinical Site (Name, Address, Phone #, Fax #)	Cliantha Research Limited 1 st floor, Silver Arcade, Near Ashwamegh III, Samrajya, Mujmahuda Road, Akota, Vadodara-390020, Gujarat, India Tel# +91-265-2324374-76, Fax# +91-265-2324378 FEI: 3007078964 DUNS : 650644367
Principal Clinical Investigator (Name, Email)	Dr. Dharit Shah, MBBS drshah@cliantha.in pi@Cliantha.in
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)	(a) 32 days from 21 May 19 to 22 Jun 19 (For Sacubitril and Valsartan) (b) -20°C ± 10°C temperature (at clinic site) -20°C ± 7°C temperature (at Bioanalytical site) (For Sacubitril and Valsartan)
Long-Term Storage Stability Coverage (no. days @ temp °C)	41 Days at -20°C ± 7°C temperature (For Sacubitril and Valsartan) 40 Days at -20°C ± 7°C temperature [For Sacubitril and Valsartan fortified with Sacubitrilat (LBQ657) and 4-Hydroxy Valsartan (1500/3000 ng/mL)]
LTSS Data Location	Module 5/ Section 5.3.1.4/ Attachment 6 (iii)/ Addendum-II to the Method Validation Report/ Section 5.2/ Page 12 (For Sacubitril and Valsartan) Module 5/ Section 5.3.1.4/ Attachment 6 (iii)/Addendum-II to the Method Validation Report/ Section 5.3/ Page 13

	[For Sacubitril and Valsartan fortified with Sacubitrilat (LBQ657) and 4-Hydroxy Valsartan (1500/3000 ng/mL)]

Table 11: Product Information (For 24 mg/26 mg)

Product	Test	Reference*
Treatment ID	T	R
Product Name	Sacubitril/Valsartan Tablets, 24 mg/26 mg	Entresto™ (Sacubitril / Valsartan) Tablets, 24 mg/26 mg
Manufacturer	(b)(4)	Distributed By: Novartis Pharmaceuticals Corp, East Hanover, NJ 07936 (b)(4)
Batch/Lot No.	ME80368 (Mother Batch # ME80340)	FX000303
Manufacture Date	Dec, 2018	N/A
Expiration Date	N/A	Feb, 2021
Strength	24 mg/26 mg	24 mg/26 mg
Dosage Form	Tablets	Tablets
Bio-batch Size	(b)(4)	N/A
Production Batch Size		N/A
Potency	Sacubitril: 101.1% Valsartan: 99.0%	Sacubitril: 100.8% Valsartan: 98.6%
Content Uniformity (mean, %CV)	Sacubitril: Mean: 102.1 %; % CV: 1.33% Valsartan: Mean: 100.7 %; %CV: 1.31%	Sacubitril: Mean: 100.7 %; % CV: 3.2 Valsartan: Mean: 99.1 %; %CV: 3.1
Dose Administered	1 × (24 mg /26 mg) Tablet	1 × (24 mg /26 mg) Tablet
Route of Administration	Oral	Oral

*Reference Standard, N/A – Not applicable

Table 12: Dropout Information – (Fasting Study # BA18086667)

Study No. BA18086667				
Subject No	Reason for dropout/replacement	Period	Replaced?	Replaced with
(b)(6)	Reason: Withdrew consent for further participation from the study. Date: [REDACTED] Time: 0737 hours	NA	Yes	(b)(6)
	Reason: Did not report for subsequent periods of the study Date: [REDACTED] Time: 0614 hours Last Treatment Received: Test	Period I	No	NA
	Reason: Adverse event (Vomiting & Dizziness) Date: [REDACTED] Time: 0847 hours Last Treatment Received: Test	Period IV	No	NA
	Reason: Protocol Violation (Found positive during alcohol breath test on check in day of period-II) Date: [REDACTED] Time: 1149 hours Last Treatment Received: Test	Period I	No	NA
	Reason: Did not report for subsequent periods of the study Date: [REDACTED] Time: 0615 hours Last Treatment Received: Reference	Period I	No	NA
	Reason: Adverse Event (Pyrexia) Date: [REDACTED] Time: 1838 hours Last Treatment Received: Reference	Period II	No	NA
	Reason: Did not report for subsequent periods of the study Date: [REDACTED] Time: 0613 hours Last Treatment Received: Reference	Period I	No	NA
	Reason: Did not report for subsequent periods of the study Date: [REDACTED] Time: 0614 hours Last Treatment Received: Reference	Period I	No	NA
	Reason: Adverse event (Pyrexia) Date: [REDACTED] Time: 1416 hours Last Treatment Received: Reference	Period I	No	NA

Table 13: Protocol Deviations – (Fasting Study # BA18086667)

Study No. BA18086667

Type	Subject # s (Test)	Subject #s (Ref.)	
Blood sample collection time deviations, Period-I	NA	(b)(6)	
Missing Blood Sample deviations, Period-I	NA		
Missing Blood Sample deviations, Period-II	(b)(6)		
Missing Blood Sample deviation, Period-III			NA
Blood sample collection time deviation, Period-IV			NA
In Period-III, 11 hours housing prior to dosing was not maintained and meal (Check-in dinner) of identical composition was not served.	NA	(b)(6)	
Post study safety assessment could not be performed and the subject was declared as lost to follow-up	NA		
Data of metabolite (Sacubitrilat) has not been included in the Final report.	NA	NA	

Table 14 (A): Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses – (Fasting Study # BA18086667) - Sacubitril

Bioequivalence Study No.BA18086667 Sacubitril										
Parameter	Standard Curve Samples									
Concentration (ng/mL)	2.500	5.000	15.00	45.00	100.0	300.0	600.0	900.0	1200	1500
* Inter day Precision (%CV)	2.4	4.3	3.7	4.5	3.4	3.7	3.7	3.3	3.5	3.7
* Inter day Accuracy (%Actual)	97.2	105	101	101	101	101	100	103	98.1	93.3
Linearity (r ² value)	0.9929291 – 0.9990540									
Linearity Range (ng/mL)	2.500 – 1500									
Sensitivity/LOQ (ng/mL)	2.500									
Bioequivalence Study No.BA18086667 Sacubitril										
Parameter	Quality Control Samples									
Concentration (ng/mL)	LQC 7.500	MQC-2 90.00	MQC-1 525.0	MQC 812.5	HQC 1125					
* Inter day Precision (%CV)	6.4	5.9	5.8	6.0	5.6					
* Inter day Accuracy (%Actual)	98.8	101	98.1	92.9	99.0					

Note: * = Results are reported as inter run

Additional quality control sample (MQC-812.5 ng/mL) was added from run 15.

Table 14 (B): Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses – (Fasting Study # BA18086667) - Valsartan

Bioequivalence Study No.BA18086667 Valsartan										
Parameter	Standard Curve Samples									
Concentration (ng/mL)	5.000	10.00	30.00	90.00	200.0	600.0	1200	1800	2400	3000
* Inter day Precision (%CV)	2.9	5.3	4.1	4.1	3.5	3.9	4.1	4.2	4.1	4.0
* Inter day Accuracy (%Actual)	97.0	106	101	100	101	101	99.3	103	97.7	94.7
Linearity (r ² value)	0.9887755 – 0.9997922									
Linearity Range (ng/mL)	5.000 – 3000									
Sensitivity/LOQ (ng/mL)	5.000									
Bioequivalence Study No.BA18086667 Valsartan										
Parameter	Quality Control Samples									
Concentration (ng/mL)	LQC 15.00	MQC-2 180.0	MQC-1 1050	MQC 1625	HQC 2250					
* Inter day Precision (%CV)	6.3	6.7	6.3	5.5	7.8					
* Inter day Accuracy (%Actual)	95.1	96.7	94.0	99.0	95.4					

Note: * = Results are reported as inter run

Additional quality control sample (MQC-1625 ng/mL) was added from run 15.

Table 15: SOP's Dealing with Bioanalytical Repeats of Study Samples –Fasting Study # BA18086667

SOP No.	Effective Date of SOP	SOP Title
(b)(4)		Sample Reanalysis and reporting criteria

4.4.1.2 Summary Tables for Pilot Fasting Study #BA17861001-01 and Pilot Fed Study #BA17861002-01 for the 97 mg/ 103 mg Strength

Table 1: Submission Summary

Drug Product Name	Sacubitril/Valsartan Tablets
Strength(s)	97 mg/103 mg

Applicant Name	Zydus Pharmaceuticals (USA), Inc.
Address	73-B, Route 31 North, Pennington, NJ 08534
Point of Contact Name	Srinivas Gurrām (Sriṇi)
Address	Zydus Pharmaceuticals (USA), Inc. 73-B, Route 31 North, Pennington, NJ 08534
Telephone Number	609-730-1900 (Ext: 110)
Fax Number	609-730-1999

Table 2(A): Summary of Bioavailability Studies – (Fasting Study # BA17861001-01) - 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)						Study Report Location
					Cmax (ng/mL)	Tmax (hr)	AUCt (ng*hr/mL)	AUCi (ng*hr/mL)	tHalf (hr)	Kel (1/hr)	
Study# BA17861001-01	To compare and evaluate the oral bioavailability of two test formulations of Sacubitril and Valsartan Tablets 97 mg/103 mg with that of ENTRESTO™ (Sacubitril and Valsartan) Tablets 97mg/103 mg in healthy, adult, human subjects under fasting conditions.	An open label, randomized, three-period, three-treatment, three sequence, crossover, balanced, single dose oral bioequivalence study.	Test Product T1 Sacubitril and Valsartan Tablets 97 mg/103 mg 1× 97 mg/103 mg, Oral, [Batch No.: 97+103-F030A]	15 dosed, 14 complete study 14 males Age: 30 (21-41) years Healthy male subjects.	5077.122 ± 1974.443 (38.889)	0.584 (0.333-3.000)	6456.314 ± 1226.039 (18.99)	6471.721 ± 1227.976 (18.974)	1.22± 0.232 (18.984)	0.587± 0.113 (19.195)	NA
			Test Product T2 Sacubitril and Valsartan Tablets 97 mg/103 mg 1× 97 mg/103 mg, Oral, [Batch No.: 97+103-F031A]		5179.69 ± 2253.767 (43.512)	0.500 (0.333-2.000)	6983.468 ± 1889.314 (27.054)	7011.15 ± 1885.878 (26.898)	1.231 ± 0.302 (24.5)	0.59± 0.123 (20.8)	
	To monitor the safety of the subjects.		Reference Product R 'ENTRESTO™' (Sacubitril and Valsartan) Tablets 97 mg/103 Mg 1× 97 mg/103 mg, Oral, [Lot No.: FX000024]		5418.419 ± 1743.975 (32.186)	0.500 (0.500-1.000)	6590.513 ± 1631.564 (24.756)	6607.417 ± 1629.802 (24.666)	1.542± 1.106 (71.755)	0.546± 0.174 (31.827)	

Notes: The mean age is calculated based on completed subjects. Tmax is presented as Median (Range).

Table 2(B): Summary of Bioavailability Studies – (Fasting Study # BA17861001-01) - 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)						Study Report Location
					Cmax (ng/mL)	Tmax (hr)	AUCt (ng*hr/mL)	AUCi (ng*hr/mL)	tHalf (hr)	Kel (1/hr)	
Study #BA17861001-01	To compare and evaluate the oral bioavailability of two test formulations of Sacubitril and Valsartan Tablets 97 mg/103 mg with that of ENTRESTO™ (Sacubitril and Valsartan) Tablets 97 mg/103 mg in healthy, adult, human subjects under fasting conditions.	An open label, randomized, three-period, three-treatment, three sequence, crossover, balanced, single dose oral bioequivalence study.	Test Product T1 Sacubitril and Valsartan Tablets 97 mg/103 mg 1x 97 mg/103 mg, Oral, [Batch No.: 97+103-F030A]	15 dosed, 14 complete d study 14 males Age: 30 (21-41) years Healthy male subjects.	4622.343 ± 969.663 (20.978)	1.750 (1.250-3.000)	29104.14 6±7733.5 6 (26.572)	29621.09 8±8021.0 12 (27.079)	10.767± 3.814 (35.426)	0.071± 0.023 (32.466)	NA
			Test Product T2 Sacubitril and Valsartan Tablets 97 mg/103 mg 1x 97 mg/103 mg, Oral, [Batch No.: 97+103-F031A]		5012.933 ± 1528.155 (30.484)	1.750 (1.000-3.000)	33856.22 8±12398.437 (36.621)	34321.51 5±12649.107 (36.855)	9.176± 1.806 (19.68)	0.078± 0.016 (19.979)	
			Reference Product R 'ENTRESTO™' (Sacubitril and Valsartan) Tablets 97 mg/103 Mg 1x 97 mg/103 mg, Oral, [Lot No.: FX000024]		4949.448 ± 1601.501 (32.357)	1.625 (1.250-3.500)	30795.31 5±12842.119 (41.702)	31222.5± 13106.86 3 (41.979)	8.83± 1.59 (18.012)	0.081± 0.015 (18.641)	

Notes: The mean age is calculated based on completed subjects. Tmax is presented as Median (Range).

Table 2(C): Summary of Bioavailability Studies – (Fed Study # BA17861002-01) - 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)						Study Report Location
					Cmax (ng/mL)	Tmax (hr)	AUCt (ng*hr/mL)	AUCi (ng*hr/mL)	tHalf (hr)	Kel (1/hr)	
Study #BA17861002-01	To compare and evaluate the oral bioavailability of two test formulations of Sacubitril and Valsartan Tablets 97 mg/103 mg with that of ENTRESTO™ (Sacubitril and Valsartan) Tablets 97 mg/103 mg in healthy, adult, human subjects under fed conditions.	An open label, randomized, three-period, three-treatment, three sequence, Cross over, balanced, single dose oral bioequivalence study.	Test Product T1 Sacubitril and Valsartan Tablets 97 mg/103 mg 1× 97 mg/103 mg, Oral, [Batch No.: 97+103-F030A]	15 dosed, 15 complete d study 15 males Age: 34 (21-42) years Healthy male subjects.	3575.26 ± 1177.328 (32.93)	1.500 (1.000-4.500)	5197.059 ± 904.947 (17.413)	5209.376 ± 906.329 (17.398)	1.029± 0.181 (17.603)	0.693± 0.12 (17.379)	NA
			Test Product T2 Sacubitril and Valsartan Tablets 97 mg/103 mg 1× 97 mg/103 mg, Oral, [Batch No.: 97+103-F031A]		3906.834 ± 1893.026 (48.454)	1.500 (0.500-4.500)	5436.987 ± 999.428 (18.382)	5450.534 ± 1000.969 (18.365)	1.087± 0.319 (29.321)	0.686± 0.186 (27.127)	
			Reference Product R 'ENTRESTO™' (Sacubitril and Valsartan) Tablets 97 mg/103 Mg 1× 97 mg/103 mg, Oral, [Lot No.: FX000024]		3401.437 ± 1182.214 (34.756)	1.750 (0.500-4.500)	5238.215 ± 1156.538 (22.079)	5252.519 ± 1157.415 (22.035)	1.078± 0.314 (29.095)	0.681± 0.149 (21.861)	

Notes: The mean age is calculated based on completed subjects. Tmax is presented as Median (Range).

Table 2(D): Summary of Bioavailability Studies – (Fed Study # BA17861002-01) - 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)						Study Report Location
					Cmax (ng/mL)	Tmax (hr)	AUCt (ng*hr/mL)	AUCi (ng*hr/mL)	tHalf (hr)	Kel (1/hr)	
Study #BA17861002-01	To compare and evaluate the oral bioavailability of two test formulations of Sacubitril and Valsartan Tablets 97 mg/103 mg with that of ENTRESTO™ (Sacubitril and Valsartan) Tablets 97 mg/103 mg in healthy, adult, human subjects under fed conditions.	An open label, randomized, three-period, three-treatment, three sequence, crossover, balanced, single dose oral bioequivalence study.	Test Product T1 Sacubitril and Valsartan Tablets 97 mg/103 mg 1x 97 mg/103 mg, Oral, [Batch No.: 97+103-F030A]	15 dosed, 15 complete d study 15 males Age: 34 (21-42) years Healthy male subjects.	2234.876 ±539.153 (24.125)	2.000 (1.500-4.500)	14593.80 ±2 5029.264 (34.462)	14894.47 ±5102.197 (34.256)	8.728± 2.499 (28.631)	0.087± 0.03 (34.898)	NA
			Test Product T2 Sacubitril and Valsartan Tablets 97 mg/103 mg 1x 97 mg/103 mg, Oral, [Batch No.: 97+103-F031A]		2514.483 ±623.126 (24.781)	2.500 (1.500-5.000)	15570.89 ±5 4671.428 (30.001)	15833.78 ±4712.035 (29.759)	9.168± 2.26 (24.652)	0.08± 0.02 (25.233)	
	To monitor the safety of the subjects.		Reference Product R 'ENTRESTO™' (Sacubitril and Valsartan) Tablets 97 mg/103 Mg 1x 97 mg/103 mg, Oral, [Lot No.: FX000024]		2445.617 ±654.834 (26.776)	3.000 (1.500-5.000)	15189.87 ±7 5378.979 (35.412)	15487.98 ±1 5456.32 (35.229)	8.791± 2.343 (26.654)	0.085± 0.026 (30.458)	

Notes: The mean age is calculated based on completed subjects. Tmax is presented as Median (Range).

Table 3(A1): Statistical Summary of the Comparative Bioavailability Data for Unscaled Average BE studies (Fasting Study # BA17861001-01) - Sacubitril

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 97 mg/103 mg (No of subjects completed= 14) 1× 97 mg/103 mg Least Square Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fasting Bioequivalence Study (BA17861001-01)						
Parameter	Test T2	N	RLD	N	Ratio	90% C.I.
AUCt	6860.067	14	6496.569	14	105.60%	(98.94%; 112.70%)
AUCi	6889.578	14	6514.663	14	105.75%	(99.19%; 112.76%)
Cmax	4720.114	14	5189.073	14	90.96%	(71.77%; 115.29%)

Table 3(A2): Statistical Summary of the Comparative Bioavailability Data for Unscaled Average BE studies (Fasting Study # BA17861001-01) - Valsartan

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 97 mg/103 mg (No of subjects completed= 14) 1× 97 mg/103 mg Least Square Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fasting Bioequivalence Study (BA17861001-01)						
Parameter	Test T2	N	RLD	N	Ratio	90% C.I.
AUCt	32429.505	14	28837.932	14	112.45%	(99.96%; 126.51%)
AUCi	32847.760	14	29204.695	14	112.47%	(99.99%; 126.51%)
Cmax	4863.220	14	4761.005	14	102.15%	(89.69%; 116.34%)

Table 3(A3): Statistical Summary of the Comparative Bioavailability Data for Unscaled Average BE studies (Fed Study # BA17861002-01) - Sacubitril

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 97 mg/103 mg (No of subjects completed= 15) 1× 97 mg/103 mg Least Square Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fed Bioequivalence Study (BA17861002-01)						
Parameter	Test T2	N	RLD	N	Ratio	90% C.I.
AUCt	5352.262	15	5120.673	15	104.52%	(99.56%; 109.74%)
AUCi	5365.802	15	5135.055	15	104.49%	(99.53%; 109.70%)
Cmax	3539.518	15	3186.444	15	111.08%	(95.39%; 129.36%)

Table 3(A4): Statistical Summary of the Comparative Bioavailability Data for Unscaled Average BE studies (Fed Study # BA17861002-01) - Valsartan

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 97 mg/103 mg (No of subjects completed= 15) 1× 97 mg/103 mg Least Square Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fed Bioequivalence Study (BA17861002-01)						
Parameter	Test T2	N	RLD	N	Ratio	90% C.I.
AUCt	14968.090	15	14269.524	15	104.90%	(96.36%; 114.18%)
AUCi	15230.511	15	14555.313	15	104.64%	(96.13%; 113.90%)
Cmax	2447.693	15	2354.550	15	103.96%	(93.26%; 115.88%)

Table 4(A): Bioanalytical Method Validation - (Fasting Study #BA17861001-01)-

Information Requested	Data
Bioanalytical method validation report location	NA
Analyte	Sacubitril
Internal standard (IS)	Sacubitril 13C4
Method description	Solid Phase Extraction with LC-ESI-MS/MS Method
Limit of quantitation	5.041 ng/mL
Average recovery of drug (%)	86.8%

Average recovery of IS (%)	94.60%
Standard curve concentrations (ng/mL)	5.041, 10.081, 240.027, 708.961, 2521.289, 3501.90, 4495.237, 5005.832
QC concentrations (ng/mL)	5.107, 15.020, 2002.715, 4005.429
QC Intraday precision range (%)	0.7-3.7
QC Intraday accuracy range (%)	96.9-111.7
QC Interday precision range (%)	1.7-4.0
QC Interday accuracy range (%)	98.4-109.2
Bench-top stability (hrs)	35hrs at room temperature
Stock stability (days)	For sacubitril and Sacubitril 13C4: Working solution and stock solution stable for 26days and 22hrs at 2-8°C and 6hrs at room temperature.
Processed stability (hrs)	75hrs at 5±3°C
Freeze-thaw stability (cycles)	5 # cycles at -70±-20°C & -30±-10°C
Long-term storage stability (days)	125 days at -70±-20°C & -30±-10°C
Dilution integrity	8912.080 diluted 1/2 and 1/5-fold
Selectivity	No interfering peaks noted in blank plasma samples

Table 4(B): Bioanalytical Method Validation - (Fasting Study #BA17861001-01) - Valsartan

Information Requested	Data
Bioanalytical method validation report location	NA
Analyte	Valsartan
Internal standard (IS)	Valsartan D9
Method description	Solid Phase Extraction with LC-ESI-MS/MS Method
Limit of quantitation	10.084 ng/mL
Average recovery of drug (%)	63.0%
Average recovery of IS (%)	67.6%
Standard curve concentrations (ng/mL)	10.084, 20.168, 480.201, 1412.355, 5044.125, 7005.729, 8993.234, 10014.737
QC concentrations (ng/mL)	10.233, 30.097, 4012.885, 8025.769
QC Intraday precision range (%)	0.8-4.3
QC Intraday accuracy range (%)	96.9-111.3
QC Interday precision range (%)	1.4-3.5
QC Interday accuracy range (%)	97.7-109.4
Bench-top stability (hrs)	35hrs at room temperature

Stock stability (days)	For Valsartan and Valsartan D9 : Working solution and stock solution stable for 26days and 22hrs at 2-8°C and 6hrs at room temperature.
Processed stability (hrs)	75hrs at 5±3°C
Freeze-thaw stability (cycles)	5 # cycles at -70±-20°C & -30±-10°C
Long-term storage stability (days)	125 days at -70±-20°C & -30±-10°C
Dilution integrity	17830.649 diluted 1/2 and 1/5-fold
Selectivity	No interfering peaks noted in blank plasma samples

Table 4(C): Bioanalytical Method Validation (Fed Study #BA17861002-01) -

Information Requested	Data
Bioanalytical method validation report location	NA
Analyte	Sacubitril
Internal standard (IS)	Sacubitril 13C4
Method description	Solid Phase Extraction with LC-ESI-MS/MS Method
Limit of quantitation	5.041 ng/mL
Average recovery of drug (%)	86.8%
Average recovery of IS (%)	94.60%
Standard curve concentrations (ng/mL)	5.041, 10.081, 240.027, 708.961, 2521.289, 3501.90, 4495.237, 5005.832
QC concentrations (ng/mL)	5.107, 15.020, 2002.715, 4005.429
QC Intraday precision range (%)	0.7-3.7
QC Intraday accuracy range (%)	96.9-111.7
QC Interday precision range (%)	1.7-4.0
QC Interday accuracy range (%)	98.4-109.2
Bench-top stability (hrs)	35hrs at room temperature
Stock stability (days)	For sacubitril and Sacubitril 13C4: Working solution and stock solution stable for 26days and 22hrs at 2-8°C and 6hrs at room temperature.
Processed stability (hrs)	75hrs at 5±3°C
Freeze-thaw stability (cycles)	5 # cycles at -70±-20°C & -30±-10°C
Long-term storage stability (days)	125 days at -70±-20°C & -30±-10°C
Dilution integrity	8912.080 diluted 1/2 and 1/5-fold
Selectivity	No interfering peaks noted in blank plasma samples

Table 4(D): Bioanalytical Method Validation (Fed Study #BA17861002-01) – Valsartan

Information Requested	Data

Bioanalytical method validation report location	NA
Analyte	Valsartan
Internal standard (IS)	Valsartan D9
Method description	Solid Phase Extraction with LC-ESI-MS/MS Method
Limit of quantitation	10.084 ng/mL
Average recovery of drug (%)	63.0%
Average recovery of IS (%)	67.6%
Standard curve concentrations (ng/mL)	10.084, 20.168, 480.201, 1412.355, 5044.125, 7005.729, 8993.234, 10014.737
QC concentrations (ng/mL)	10.233, 30.097, 4012.885, 8025.769
QC Intraday precision range (%)	0.8-4.3
QC Intraday accuracy range (%)	96.9-111.3
QC Interday precision range (%)	1.4-3.5
QC Interday accuracy range (%)	97.7-109.4
Bench-top stability (hrs)	35hrs at room temperature
Stock stability (days)	For Valsartan and Valsartan D9 : Working solution and stock solution stable for 26days and 22hrs at 2-8°C and 6hrs at room temperature.
Processed stability (hrs)	75hrs at 5±3°C
Freeze-thaw stability (cycles)	5 # cycles at -70±-20°C & -30±-10°C
Long-term storage stability (days)	125 days at -70±-20°C & -30±-10°C
Dilution integrity	17830.649 diluted 1/2 and 1/5-fold
Selectivity	No interfering peaks noted in blank plasma samples

Table 5 Summary of In Vitro Dissolution Studies: Sacubitril/Valsartan Tablets, 97 mg/103 mg [Reference product (Lot: FX000024)] vs. Test product (Batch No.: 97+103-F031A)1 - Sacubitril

Dissolution Conditions		Apparatus:		Speed of Rotation:		Medium:		Volume:		Temperature:	
		(b)(4)									
Firm's Proposed Specifications		(b)(4)									
Dissolution Testing Site (Name, Address)		(b)(4)									
Study Ref No.	Testing Date	Product ID\Batch No. (Reference - Exp. Dt.) (Test - Mfg Dt.)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes)				Study Report Location		
					10	15	20	30	45		
Study Report	April 22, 2018	Entresto™ Sacubitril/valsartan tablets, 97 mg/103 mg Batch Number: FX000024 Expiry date: May, 2020 Distributed by: Novartis pharmaceuticals corp, East Hanover, NJ07936	97 mg/103 mg, Tablets	6	Mean	49.9	69.3	82.8	93.2	96.1	NA
					Range	(b)(4)					
					%CV	15.7	13.9	12.5	5.0	1.7	
Study Report	April 22, 2018	Sacubitril/Valsartan Tablets, 97 mg/103 mg Batch Number: 97+103-F031A Mfg. date: April, 2018	97 mg/103 mg, Tablets	6	Mean	55.9	78.2	91.9	99.2	99.7	NA
					Range	(b)(4)					
					%CV	10.2	5.2	4.5	0.8	0.9	

Table 5 Summary of In Vitro Dissolution Studies: Sacubitril/Valsartan Tablets, 97 mg/103 mg [Reference product (Lot: FX000024)] vs. Test product (Batch No.: 97+103-F031A)] - Valsartan

Dissolution Conditions		Apparatus:		Speed of Rotation:		Medium:		Volume:		Temperature:	
		(b)(4)									
Firm's Proposed Specifications		(b)(4)									
Dissolution Testing Site (Name, Address)		(b)(4)									
Study Ref No.	Testing Date	Product ID\Batch No. (Reference - Exp. Dt.) (Test - Mfg Dt.)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes)				Study Report Location		
Study Report	April 22, 2018	Entresto™ Sacubitril/valsartan tablets, 97 mg/103 mg Batch Number: FX000024 Expiry date: May, 2020 Distributed by: Novartis pharmaceuticals corp, East Hanover, NJ07936	97 mg/103 mg, Tablets	6	Mean	50.4	69.8	83.5	93.9	96.8	NA
					Range	(b)(4)					
Study Report	April 22, 2018	Sacubitril/Valsartan Tablets, 97 mg/103 mg Batch Number: 97+103-F031A Mfg. date: April, 2018	97 mg/103 mg, Tablets	6	%CV	15.5	13.7	12.3	4.8	1.6	NA
					Mean	56.7	78.1	93.0	100.4	100.8	
		(b)(4)			Range	(b)(4)					
					%CV	9.9	5.1	4.4	0.7	1.0	

Table 6 Formulation Data

Sr. No.	Ingredient	Batch no.: 97+103-F031A Batch size: 1,500 tablets	
		mg / tablet	% w/w
(b)(4)			
	Sacubitril/Valsartan *	(b)(4)	
	Microcrystalline Cellulose NF (b)(4)		
	Low-substituted Hydroxypropyl Cellulose NF (b)(4)		
	Colloidal Silicon Dioxide NF (b)(4)		
	Sodium Stearyl Fumarate NF (b)(4)		
(b)(4)			
Total		402.000	100.00
(b)(4)			

Table 7(A): Demographic Profile of Subjects Completing the Bioequivalence Study – Fasting Study #BA17861001-01

Study No. BA17861001-01			
		Treatment Groups	
		Test Product (T2) N = 14	Reference Product (R) N = 14
Age (years)	Mean ± SD	30 ± 7	30 ± 7
	Range	21 - 41	21 - 41
Age Groups	< 18	0 (0.00%)	0 (0.00%)
	18 – 40	12 (85.71%)	12 (85.71%)
	41 – 64	02 (14.29%)	02 (14.29%)
	65 – 75	0 (0.00%)	0 (0.00%)
	> 75	0 (0.00%)	0 (0.00%)
Sex	Male	14 (100.00%)	14 (100.00%)

	Female	0 (0.00%)	0 (0.00%)
Race	Asian	14 (100.00%)	14 (100.00%)
	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 (Kg/m ²)	Mean ± SD	22.5 ± 3.2	22.5 ± 3.2
	Range	18.8 – 29.1	18.8 – 29.1
Tobacco users	Yes	0 (0.00%)	0 (0.00%)
	No	14 (100.00%)	14 (100.00%)

Table 7(B): Demographic Profile of Subjects Completing the Bioequivalence Study – Fed Study #BA17861002-01

Study No. BA17861002-01			
		Treatment Groups	
		Test Product (T2) N = 15	Reference Product (R) N = 15
Age (years)	Mean ± SD	34 ± 6	34 ± 6
	Range	21 - 42	21 - 42
Age Groups	< 18	0 (0.00%)	0 (0.00%)
	18 – 40	13 (86.67%)	13 (86.67%)
	41 – 64	02 (13.33%)	02 (13.33%)
	65 – 75	0 (0.00%)	0 (0.00%)
	> 75	0 (0.00%)	0 (0.00%)
Sex	Male	15 (100.00%)	15 (100.00%)
	Female	0 (0.00%)	0 (0.00%)
Race	Asian	15 (100.00%)	15 (100.00%)
	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 (Kg/m ²)	Mean ± SD	24.3 ± 3.5	24.3 ± 3.5
	Range	19.1 – 29.6	19.1 – 29.6
Tobacco users	Yes	0 (0.00%)	0 (0.00%)
	No	15 (100.00%)	15 (100.00%)

**Table 8(A): Incidence of Adverse Events in Individual Studies - Fasting Study
#BA17861001-01**

(1) Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Bioequivalence Study Study No.	
	Test (T2) (2) N=14 (3) n (%)	Reference (R) (2) N=15 (3) n (%)
Investigations		
White blood cell count increased	1 (7.14%)	0 (0.00%)
Total	1 (7.14%)	0 (0.00%)

(1) MedDRA Version 21.0

(2) N=Number of subjects dosed for each treatment

(3) n= Number of subjects reporting at least one incidence of respective adverse event; (%)=percentage of subjects reporting at least one incidence of respective adverse event

**Table 8(B): Incidence of Adverse Events in Individual Studies - Fed Study
#BA17861002-01**

(1) Body System / Adverse Event	Reported Incidence by Treatment Groups	
	ed Bioequivalence Study Study No.	
	Test (T2) (4) N=15 (5) n (%)	Reference (R) (2) N=15 (3) n (%)
Investigations		
Eosinophil count increased	0 (0.00%)	1 (6.67%)
Total	0 (0.00%)	1 (6.67%)

(1) MedDRA Version 21.0

(2) N=Number of subjects dosed for each treatment

(3) n= Number of subjects reporting at least one incidence of respective adverse event; (%)=percentage of subjects reporting at least one incidence of respective adverse event

Table 9(A): Reanalysis of Study Samples - Fasting Study # (Sacubitril)

Study No. BA17861001-01 Sacubitril						
Reason why assay was repeated	Number of samples reanalyzed		% of total assays		Number of recalculated values used after reanalysis	
	Actual number		Actual number		% of total assays	
	T2	R	T2	R	T2	R
Pharmacokinetic	0.0	0.0	0.00	0.00	0.0	0.00
Dilution Integrity	5.0	9.0	1.49	2.50	0.0	0.00
Internal Standard Variation	0.0	1.0	0.00	0.28	0.0	0.28
Total	5.0	10.0	1.49	2.78	0.0	0.28

Total No. of Samples assayed=982

Total no. of samples assayed for test Product (T1) =287

Total no. of samples assayed for test Product (T2) =336

Total no. of samples assayed for Reference Product (R)=359

Table 9(B): Reanalysis of Study Samples - Fasting Study # (Valsartan)

Study No. BA17861001-01 Valsartan						
Reason why assay was repeated	Number of samples reanalyzed		% of total assays		Number of recalculated values used after reanalysis	
	Actual number		Actual number		% of total assays	
	T2	R	T2	R	T2	R
Pharmacokinetic	0.0	0.0	0.00	0.00	0.0	0.00
Dilution Integrity	0.0	0.0	0.00	0.00	0.0	0.00
Internal Standard Variation	0.0	0.0	0.00	0.00	0.0	0.00
Total	0.0	0.0	0.00	0.00	0.0	0.00

Table 9(C): Reanalysis of Study Samples - Fed Study # (Sacubitril)

Study No. BA17861002-01 Sacubitril								
Reason why assay was repeated	Number of samples reanalyzed		Number of recalculated values used after reanalysis		Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T2	R	T2	R	T2	R	T2	R
Pharmacokinetic	0.0	0.0	0.00	0.00	0.0	0.0	0.00	0.00
Dilution Integrity	2.0	1.0	0.53	0.27	1.0	0.0	0.27	0.00
Internal Standard Variation	1.0	0.0	0.27	0.00	0.0	0.0	0.00	0.00
Pre dose	0.0	0.0	0.00	0.27	0.0	0.0	0.00	0.00
Total	3.0	1.0	0.80	0.54	0.0	0.0	0.27	0.00

Table 9(D): Reanalysis of Study Samples - Fed Study # (Valsartan)

Study No. BA17861002-01 Valsartan								
Reason why assay was repeated	Number of samples reanalyzed		Number of recalculated values used after reanalysis		Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T2	R	T2	R	T2	R	T2	R
Pharmacokinetic	0.0	0.0	0.0	0.0	0.0	0.0	0.00	0.00
Dilution Integrity	0.0	0.0	0.0	0.0	0.0	0.0	0.00	0.00
Internal Standard Variation	0.0	0.0	0.0	0.0	1.0	0.0	0.27	0.00
Pre dose	0.0	0.0	0.0	0.0	0.0	0.0	0.00	0.00
Total	0.0	0.0	0.0	0.0	0.0	0.0	0.27	0.00

Total No. of Samples assayed=1123

Total no. of samples assayed for test Product (T1) =375
Total no. of samples assayed for test Product (T2) =375
Total no. of samples assayed for Reference Product (R) =373

Table 10(A): Study Information - Fasting Study # BA17861001-01

Study Number	BA17861001-01			
Study Title	Single dose oral bioequivalence pilot study of two test formulations of Sacubitril and Valsartan Tablets 97 mg/103 mg and 'ENTRESTO™' (Sacubitril and Valsartan) Tablets 97 mg/103 mg in healthy adult human subjects under fasting conditions.			
Study Type	☒ In Vivo BE	☐ In Vitro BE	☐ Permeability	☐ Other
Submission Location:	Not Applicable			
Study Report	Not Applicable			
Validation Report	Not Applicable			
Bioanalytical Report	Not Applicable			
Clinical Site (Name, Address, Phone #, Fax#)	Cliantha Research Limited 1 st floor, Silver Arcade, Near Ashwamegh III, Samrajya, Mujmahuda Road, Akota, Vadodara-390020, Gujarat, India Tel# +91-265-2324374-76, Fax# +91-265-2324378 FEI: 3007078964 DUNS : 650644367			
Principal Investigator (Name, Email)	Dr. Bhargav Ramanandi, MBBS bramanandi@cliantha.in pi@Cliantha.in			
Analytical Site (Name, Address, Phone #, Fax#)	(b)(4)			
Analysis Dates	Sacubitril and Valsartan :22/05/18- 30/05/18			
Principal Analytical Investigator (Name, Email)	(b)(4)			
Sample Storage:				
(a) Duration (no. of days from the first day of sample collection to the last day of sample analysis)	(a) 30 days from 01/05/18 to 30/05/18 for Sacubitril and Valsartan			
(b) Temperature Range (e.g., -20°C to -80 °C)	(b) -70±-20°C & -30±-10°C			
Long -Term Storage Stability Coverage (no.days @temp °C)	Not applicable			

Table 10(B): Study Information - Fed Study # BA17861002-01

Study Number	BA17861002-01
Study Title	Single dose oral bioequivalence pilot study of two test formulations of Sacubitril and Valsartan Tablets 97 mg/103 mg and 'ENTRESTO™' (Sacubitril and Valsartan) Tablets 97 mg/103 mg in healthy adult human subjects under fed conditions.

Study Type	☒ In Vivo BE	☐ In Vitro BE	☐ Permeability	☐ Other
Submission Location: Study Report Validation Report Bioanalytical Report	Not Applicable			
	Not Applicable			
	Not Applicable			
Clinical Site (Name, Address, Phone #, Fax#)	Cliantha Research Limited 1 st floor, Silver Arcade, Near Ashwamegh III, Samrajya, Mujmahuda Road, Akota, Vadodara-390020, Gujarat, India Tel# +91-265-2324374-76, Fax# +91-265-2324378 FEI: 3007078964 DUNS : 650644367			
Principal Investigator (Name, Email)	Dr. Bhargav Ramanandi, MBBS bramanandi@cliantha.in ni@Cliantha.in			
Analytical Site (Name, Address, Phone #, Fax#)	(b)(4)			
Analysis Dates	Sacubitril and Valsartan :29/05/18- 05/06/18			
Principal Analytical Investigator (Name, Email)	(b)(4)			
Sample Storage: (b) 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)	(c) 35 days from 01/05/18 to 05/06/18 for Sacubitril and Valsartan (d) -70±-20°C & -30±-10°C			
Long -Term Storage Stability Coverage (no.days @temp °C)	Not applicable			

Table 11(A): Product Information

Product	Test	Reference
Treatment ID	T	R
Product Name	Sacubitril/Valsartan Tablets, 97 mg/103 mg	Entresto™ (Sacubitril / Valsartan) Tablets, 97 mg/103 mg
Manufacturer	(b)(4)	<u>Distributed By:</u> Novartis Pharmaceuticals Corp, East Hanover, NJ 07936 (b)(4)

		Pharmaceutical Manufacturing, Pte Ltd 637461 Singapore
Batch/Lot No.	97+103-F031A	FX000024
Manufacture Date	April 2018	N/A
Expiration Date	N/A	May 2020
Strength	97 mg/103 mg	97 mg/103 mg
Dosage Form	Tablets	Tablets
Bio-batch Size		N/A
Production Batch Size	(b)(4)	N/A
Potency	Sacubitril: 100.9% Valsartan: 102.9%	Sacubitril: 101.2% Valsartan: 99.1%
Content Uniformity (mean, %CV)	Sacubitril: Mean – 100.8%, %CV – 1.2% Valsartan: Mean – 103.0%, %CV – 1.2%	Sacubitril: Mean: 102.4 %; AV: 2.5 Valsartan: Mean: 101.0 %; AV: 1.5
Dose Administered	1 × (97 mg / 103 mg) Tablet	1 × (97 mg / 103 mg) Tablet
Route of Administration	Oral	Oral

N/A: Not applicable

Table 12(A): Dropout Information – Fasting Study # BA17861001-01

Study No.				
Subject No	Reason for dropout/replacement	Period	Replaced?	Replaced with
(b)(6)	Reason: Withdrew his consent for further participation in the study. Date: (b)(6) Time: 0855 hours Last Treatment Received: NA	NA	Yes	(b)(6)
	Reason: Did not report for subsequent period of the study. Date: (b)(6) Time: 0556 hours Last Treatment Received: Reference	Period I	No	NA
	Reason: Withdrawal by subject. Date: (b)(6) Time: 1430 hours Last Treatment Received: Reference	Period I	No	NA
	Reason: Found positive during Alcohol breath test on check-in day of period III. Date: (b)(6) Time: 1133 hours Last Treatment Received: Reference	Period II	No	NA
(b)(6)				

* Subject# [] was discontinued for period II only and Subject# [] was discontinued for period III only.

Table 12(B): Dropout Information - Fed Study # BA17861002-01

Study No.				
Subject No	Reason for dropout/replacement	Period	Replaced?	Replaced with
(b)(6)	Reason: Withdrew his consent for further participation in the study. Date: [] Time: 0849 hours Last Treatment Received: NA	NA	Yes	(b)(6)

Table 13(A): Protocol Deviations - Fasting Study # BA17861001-01

Study No.		
Type	Subject #s (Test 2)	Subject #s (Ref.)
Blood Sample collection time deviations, Period I	NA	NA
Missed blood sample collections, Period I	NA	(b)(6)
Blood Sample collection time deviations, Period II	(b)(6)	(b)(6)
Missed blood sample collections, Period II	NA	NA
Blood Sample collection time deviations, Period III	(b)(6)	NA
Missed blood sample collections, Period III	(b)(6)	NA

Note: Superscript above the subject number indicates the number of multiple occurrences of the indicated deviation recorded by that subject.

Table 13(B): Protocol Deviations - Fed Study # BA17861002-01

Study No.		
Type	Subject #s (Test 2)	Subject #s (Ref.)
Blood Sample collection time deviations, Period I	NA	NA
Missed blood sample collections, Period I	NA	NA
Blood Sample collection time deviations, Period II	(b)(6)	(b)(6)
Missed blood sample collections, Period II	NA	(b)(6)
Blood Sample collection time deviations, Period III	NA	(b)(6)
Missed blood sample collections, Period III	(b)(6)	NA

Note: Superscript above the subject number indicates the number of multiple occurrences of the indicated deviation recorded by that subject.

Table 14 (A): Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses - Fasting Study #BA17861001-01 (Sacubitril)

Bioequivalence Study No. BA17861001-01 Sacubitril								
Parameter	Standard Curve Samples							
Concentration (ng/mL)	5.114	10.228	239.729	705.084	2518.158	3497.442	4489.656	4999.616
Inter day Precision (%CV)	1.1	2.2	1.0	0.9	0.9	1.3	0.9	1.0

Inter day Accuracy (%Actual)	99.6	100.8	100.0	100.5	100.7	100.1	99.1	99.1
Linearity	0.9998-1.000							
Linearity Range (ng/mL)	5.114-4999.616							
Sensitivity/LOQ (ng/mL)	5.114							

Bioequivalence Study No. BA17861001-01 Sacubitril			
Parameter	Quality Control Samples		
Concentration (ng/mL)	LQC 15.028	MQC 2003.784	HQC 4007.568
Inter day Precision (%CV)	3.8	1.5	1.5
Inter day Accuracy (%Actual)	98.3	101.8	99.9

Table 14 (B): Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses - Fasting Study #BA17861001-01 (Valsartan)

Bioequivalence Study No. BA17861001-01 Valsartan								
Parameter	Standard Curve Samples							
Concentration (ng/mL)	10.212	20.424	478.679	1407.879	5028.138	6983.524	8964.730	9982.995
Inter day Precision (%CV)	1.3	2.5	1.0	2.0	1.2	1.2	1.3	1.0
Inter day Accuracy (%Actual)	99.0	101.9	101.0	101.0	100.3	100.2	98.3	98.4
Linearity	0.9992-1.000							
Linearity Range (ng/mL)	10.212-9982.995							
Sensitivity/LOQ (ng/mL)	10.212							

Bioequivalence Study No. BA17861001-01 Valsartan			
Parameter	Quality Control Samples		
Concentration (ng/mL)	LQC 30.092	MQC 4012.202	HQC 8024.405
Inter day Precision (%CV)	3.7	1.9	1.7
Inter day Accuracy (%Actual)	95.0	97.0	94.6

Table 14 (C): Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses - Fed Study #BA17861002-01 (Sacubitril)

Bioequivalence Study No. BA17861002-01 Sacubitril	
Parameter	Standard Curve Samples

Concentration (ng/mL)	5.114	10.228	239.729	705.084	2518.158	3497.442	4489.656	4999.616
Inter day Precision (%CV)	1.5	3.0	1.5	1.4	1.2	1.3	1.7	0.8
Inter day Accuracy (%Actual)	99.9	100.3	100.1	100.3	100.8	100.3	99.1	99.3
Linearity	0.9994-1.0000							
Linearity Range (ng/mL)	5.114-4999.616							
Sensitivity/LOQ (ng/mL)	5.114							

Bioequivalence Study No. BA17861002-01 Sacubitril			
Parameter	Quality Control Samples		
Concentration (ng/mL)	LQC 15.028	MQC 2003.784	HQC 4007.568
Inter day Precision (%CV)	2.7	3.7	1.6
Inter day Accuracy (%Actual)	99.0	102.2	101.4

Table 14 (D): Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses - Fed Study #BA17861002-01 (Valsartan)

Bioequivalence Study No. BA17861002-01 Valsartan								
Parameter	Standard Curve Samples							
Concentration (ng/mL)	10.212	20.424	478.679	1407.879	5028.138	6983.524	8964.730	9982.995
Inter day Precision (%CV)	1.2	2.4	1.7	1.0	1.3	1.7	1.6	1.1
Inter day Accuracy (%Actual)	100.0	99.9	101.0	100.4	100.2	100.0	99.2	99.3
Linearity	0.9995-1.0000							
Linearity Range (ng/mL)	10.212-9982.995							
Sensitivity/LOQ (ng/mL)	10.212							

Bioequivalence Study No. BA17861002-01 Valsartan			
Parameter	Quality Control Samples		
Concentration (ng/mL)	LQC 30.092	MQC 4012.202	HQC 8024.405
Inter day Precision (%CV)	3.3	4.0	1.7
Inter day Accuracy (%Actual)	94.9	97.4	96.3

Table 15 SOP's Dealing with Bioanalytical Repeats of Study Samples - Fasting Study # and Fed Study #BA17861002-01

SOP No.	Effective Date of SOP	SOP Title
(b)(4)		Analytical batch organization and Analytical batch acceptance criteria for method validation and study sample analysis

(b)(4)

Procedure for Re-injection and Repeat analysis

Table 16(B): Composition of Non-Standard Breakfast Meal Used in Fed Bioequivalence Study - Fed Study #BA17861002-01

Standard FDA Meal Used?		☐ Yes ☒ No				
If No, then meal components and composition is listed in the table below						
Composition of Non-standard FDA Meal Used in Fed Bioequivalence Study						
Ingredients		Amount*	Energy	Protein	Fats	Carbohydrate
		(gm)	(kcal)	(kcal)	(kcal)	(kcal)
MILK (STERILISED FLAVOURED)	Milk	250 ml	221.750	32.000	69.750	120.000
CHICKEN DANA	Chicken	70 gm	120.036	63.336	56.700	0.000
	Refined flour	20 gm	69.072	8.288	1.368	59.416
	Oil	20 ml	180.000	0.000	180.000	0.000
BREAD BUTTER	Bread	20 gm	49.020	6.24	1.260	41.520
	Butter	10 gm	72.200	0.200	72.000	0.000
POTATO CHAAT	Potato	40 gm	27.116	2.464	0.828	23.824
	Oil	5 ml	45.000	0.000	45.000	0.000
PANEER	Paneer	15 gm	38.713	11.316	19.953	7.444
	Oil	2 ml	18.000	0.000	18.000	0.000
BOILED EGG MASALA	Egg	50 gm	84.780	26.280	58.500	0.000
TOTAL			925.687	50.124	523.359	252.204
PERCENTAGE			NA	16.218	56.537	27.245

*Quantity of Raw Ingredients

4.4.2 SAS Output

Study	Analyte	SAS Data	SAS Code	SAS Stat	SAS Output/Table
Fasting (97 mg/103 mg strength)	Sacubitril	To be analyzed upon receipt of additional information from the applicant			
	Valsartan				
Fed (97 mg/103 mg strength)	Sacubitril	 213719_Fed_Datasets_Sacubitril.doc	 TWOWAYCALCKE fed sacub 12hr.SAS	 213719_Fed_stat_SacubitrilACTUAL.doc	 213719_Fed_table_SacubitrilACTUAL.doc
	Valsartan	 213719_Fed_Datasets_Valsartan.doc	 TWOWAYCALCKE fed valsar.SAS	 213719_Fed_stat_ValsartanACTUAL.doc	 213719_Fed_table_ValsartanACTUAL.doc

NOTE TO DBI PROJECT MANAGER and REGULATORY PROJECT MANAGER (RPM): As per OGD Policy, a Citizen Petition (CP) is pending for this drug product which states the following:

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

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

Citizen petition (FDA-2019-P-2869) for Multiple drug products containing valsartan, which requests FDA to: 1) review and significantly lower the acceptable intake/permitted daily exposure limit of DMF, as listed in the current FDA guidance Q3C – Tables and List, Guidance for Industry, from its current level of 8,800,000 nanograms to less than 1,000 nanograms (and potentially as low as 96 nanograms); 2) request a recall of identified lots of valsartan on the basis that, due to contamination with a probable human carcinogen, these drugs are adulterated under Section 501 of the FDCA (21 U.S.C. § 351) and misbranded under Section 502 of the FDCA (21 U.S.C. § 352); 3) conduct examinations and investigation under Section 702 (a) of the FDCA (21 U.S.C. § 372(a)) regarding these products, their manufacturing processes, and the manufacturer submissions made for FDA approval under 704 (a) of the FDCA (21 U.S.C. § 374(a)) and effect labeling revisions as needed

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

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 213719
APPLICANT: Zydus Pharmaceuticals (USA) Inc.
DRUG PRODUCT: Sacubitril/Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg

The Division of Bioequivalence I (DBI) has completed its review and has identified the following deficiencies:

Pharmacokinetic (PK) Bioequivalence (BE) Studies

Deficiency Related to Pre-Study Method Validation

1. Please specify what anticoagulant was used in Addendum-I of your method validation AP LC/MS/MS 528.MV.001 (7/8/2019 submission, Module 5.3.1.4 BA17861024-01...\attachment-6-2-addendum-1-method-val-reports).

Deficiency Related to Fasting Study BA18086532

2. The Agency acknowledges that you provided SAS .xpt datasets for subjects that completed all 4 periods of the study (7/8/2019 submission, Module 5.3.1.2. BA18086532...\Data Analysis Data\Analysis Dataset Legacy\pk-sacubitril.xpt, \raw-sacubitril.xpt, \pk-valsartan.xpt, and \raw-valsartan/xpt). Please update your SAS .xpt datasets to also include data from all discontinued subjects (i.e., Subjects

Sincerely yours,

Utpal Munshi, Ph.D.
Acting Director, Division of Bioequivalence I
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

4.5 Outcome Page

Completed Assignment for 213719 ID: 40835

Reviewer: Ma, Tian

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

Items:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Score</i>	<i>Subtotal</i>		
40835	7/8/2019	BIO	ANDA Original [1]	1	1	Edit	Delete
40835	7/8/2019	Parallel	Fasting Study [1]	1	1	Edit	Delete
40835	7/8/2019	Parallel	Fasting Study (Additional Analyte) [0.25]	0.25	0.25	Edit	Delete
40835	7/8/2019	Parallel	Fed Study [1]	1	1	Edit	Delete
40835	7/8/2019	Parallel	Fed Study (Additional Analyte) [0.25]	0.25	0.25	Edit	Delete
40835	7/8/2019	Parallel	Dissolution-Based Waiver (IR) (For all waiver strengths) [0.25]	0.25	0.25	Edit	Delete
40835	7/8/2019	Parallel	Pilot and Failed Full Extra Study for the Same Formulation as the Proposed Formulation (as defined in Guidance) [0.25]	0.75	0.75	Edit	Delete
				Total:	4.5		

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 213719

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS



ANDA 213719

AMENDMENT ACKNOWLEDGEMENT
Standard
Major

Zydus Pharmaceuticals (USA) Inc.
73-B, Route 31 North
Pennington, NJ 08534
Attention: Srinivas Gurram
Senior Vice President- Head of Regulatory Affairs and CQA Lead- Americas

Dear Srinivas Gurram:

This is in reference to your amendment received on June 14, 2022, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Sacubitril/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 13, 2023. If this standard major amendment requires an inspection, the goal date for review of this standard major amendment is April 13, 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 Gwendolyn Murphy, Regulatory Project Manager, at (240) 402 - 9624.

Sincerely,

{See appended electronic signature page}

Gwendolyn Murphy
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration



Gwendolyn
Murphy

Digitally signed by Gwendolyn Murphy

Date: 6/15/2022 11:14:58AM

GUID: 542af06d01243746ca2493dc5935bd01



ANDA 213719

COMPLETE RESPONSE

Zydus Pharmaceuticals (USA) Inc.
73-B, Route 31 North
Pennington, NJ 08534
Attention: Srinivas Gurram
Sr. VP-Head of Regulatory and CQA - Americas

Dear Srinivas Gurram:

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/Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg.

We acknowledge receipt of the September 21, 2021 submission, which constituted a complete response to our August 25, 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

Manufacturing

The Pharmaceutical Quality deficiencies have been classified as MAJOR because one or more facilities were found inadequate at the time of action due to inspectional deficiencies as noted in Appendix A, Section A(6)(a) of the Guidance for Industry, ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). Note that after the deficiencies have been purportedly resolved, FDA must assess the resolution of the cited deficiencies during the next review cycle. This assessment, upon receipt of an amendment responding to this deficiency, in FDA's judgement, will require substantial expenditure of FDA resources.

(b)(4)

(b)(4)

LABELING

1. GENERAL COMMENTS

(b)(4)

2. PRESCRIBING INFORMATION

a. INDICATIONS AND USAGE, Revise Section 1.1 Adult Heart Failure as follows:

(b)(4)

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

b. ADVERSE REACTIONS, Clinical Trials Experience, section 6.1

(b)(4)
"A total of 6,622...at least 1 year."
(b)(4)

3. PATIENT INFORMATION LEAFLET

Revise the "What are sacubitril and valsartan tablets?" section to read as follows:

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 Tablets work better when the heart cannot pump a normal amount of blood to the body.

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

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/DRUG PRODUCT/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
MANUFACTURING/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 Gwendolyn Murphy, Regulatory Project Manager, Division of Project Management, at (240) 402 - 9624.

Sincerely yours,

{See appended electronic signature page}

For Denise P. Toyer McKan, PharmD
Director, Division of Project Management
Office of Regulatory Operations
Office of Generic Drugs

¹ Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).



Mandy
Kwong

Digitally signed by Mandy Kwong

Date: 5/09/2022 12:14:04PM

GUID: 529372550000cc96a0a98e57d06862e5



ANDA 213719

AMENDMENT ACKNOWLEDGEMENT
Standard
Major

Zydus Pharmaceuticals (USA) Inc.
73-B, Route 31 North
Pennington, NJ 08534
Attention: Srinivas Gurram
Vice President and Head of Regulatory & Quality Affairs - North America

Dear Sir:

This is in reference to your amendment received on September 21, 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 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 May 20, 2022. If this standard major amendment requires an inspection, the goal date for review of this standard major amendment is July 20, 2022. Two possible goal dates are provided because FDA is unable to determine if an amendment requires an inspection at the time of submission. FDA will make this determination during the assessment of the amendment. For information, see FDA's guidance for industry, *ANDA Submissions - Amendments to Abbreviated New Drug Applications Under GDUFA*.

GDUFA II provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the RLD that occur after the submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure your application stays up to date with the Agency's current recommendations on demonstrating bioequivalence reflected in relevant product specific guidances.

If you have any questions, contact Gwendolyn Murphy, Regulatory Project Manager, at (240) 402 - 9624.

Sincerely,

{See appended electronic signature page}

Gwendolyn Murphy
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration



Gwendolyn
Murphy

Digitally signed by Gwendolyn Murphy

Date: 9/22/2021 01:18:02PM

GUID: 542af06d01243746ca2493dc5935bd01



ANDA 213719

COMPLETE RESPONSE

Zydus Pharmaceuticals (USA) Inc.
73-B, Route 31 North
Pennington, NJ 08534
Attention: Srinivas Gurram
Vice President & Head of Regulatory and Quality Affairs - North America

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 December 28, 2020 submission, which constituted a complete response to our July 9, 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

(b)(4)

Manufacturing

The Pharmaceutical Quality deficiencies have been classified as MAJOR because one or more facilities were found inadequate at the time of action due to inspectional deficiencies as noted in Appendix A, Section A(6)(a) of the Guidance for Industry, ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). Note that after the deficiencies have been purportedly resolved, FDA must assess the resolution of the cited deficiencies during the next review cycle.

This assessment, upon receipt of an amendment responding to this deficiency, in FDA's judgement, will require substantial expenditure of FDA resources.

(b)(4)

DRUG PRODUCT/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/MANUFACTURING**

Upon review of your amendment, FDA may identify information in the amendment that may require a change in classification and an adjustment to the goal date.

Within one year after the date of this letter, you are required to respond by taking one of the actions available under 21 CFR 314.110(b). If you do not take one of these actions, we may consider your lack of response as a request to withdraw the ANDA under 21 CFR 314.110(c)(1). You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter does not fulfill the requirements in 21 CFR 314.110(b)(1) and therefore will not be processed as a resubmission and will not start a new review cycle.

The drug product may not be marketed without final Agency approval under section 505(j) of the FD&C Act.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions¹ with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection

prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self-identification or fee payment.

GDUFA II provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including by fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the RLD that occur after submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure you stay up to date with the Agency's current thinking on topics through guidances for industry, including product-specific guidances.

If you have any questions, call Gwendolyn Murphy, Regulatory Project Manager, Division of Project Management, at (240) 402 - 9624.

Sincerely yours,

{See appended electronic signature page}

For Denise P. Toyer McKan, PharmD
Director, Division of Project Management
Office of Regulatory Operations
Office of Generic Drugs

¹ Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).



Aaron
Sigler

Digitally signed by Aaron Sigler

Date: 8/25/2021 08:24:21AM

GUID: 508da6fa0002827f1a9f2526d1b2cc69



ANDA 213719

AMENDMENT ACKNOWLEDGEMENT
Standard
Major

Zydus Pharmaceuticals (USA) Inc.
73-B, Route 31 North
Pennington, NJ 08534
Attention: Srinivas Gurram
Vice President & Head of Regulatory and Quality Affairs - North America

Dear Sir:

This is in reference to your amendment received on December 28, 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 August 27, 2021. If this standard major amendment requires an inspection, the goal date for review of this standard major amendment is October 27, 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*.

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If you have any questions, contact Gwendolyn Murphy, Regulatory Project Manager, at (240) 402 - 9624.

Sincerely,

{See appended electronic signature page}

Gwendolyn Murphy
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration



Gwendolyn
Murphy

Digitally signed by Gwendolyn Murphy

Date: 12/31/2020 11:31:32AM

GUID: 542af06d01243746ca2493dc5935bd01



ANDA 213719

COMPLETE RESPONSE

Zydus Pharmaceuticals (USA) Inc.
73-B, Route 31 North
Pennington, NJ 08534
Attention: Srinivas Gurram
Vice President & Head of Regulatory and Quality Affairs - North America

Dear Sir:

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

Reference is also made to any amendments submitted prior to the issuance of this letter.

We have completed our review of this ANDA, as amended, and have determined that we cannot approve this ANDA in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PHARMACEUTICAL QUALITY

Drug Substance

- 1.
2. (b)(4)

Drug Product

3.

4.

5.

(b)(4)

6.

Facility Inspection

The Pharmaceutical Quality deficiencies have been classified as MAJOR because one or more facilities were found inadequate at the time of action due to inspectional deficiencies as noted in Appendix A, Section A(6)(a) of the Guidance for Industry, ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). Note that after the deficiencies have been purportedly resolved, FDA must assess the resolution of the cited deficiencies during the next review cycle. This assessment, upon receipt of an amendment responding to this deficiency, in FDA's judgement, will require substantial expenditure of FDA resources.

7.

8.

(b)(4)

9.

(b)(4)

PROCESS/BIPHARMACEUTICS/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:

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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. 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/FACILITY INSPECTION**

Upon review of your amendment, FDA may identify information in the amendment that may require a change in classification and an adjustment to the goal date.

Within one year after the date of this letter, you are required to respond by taking one of the actions available under 21 CFR 314.110(b). If you do not take one of these actions, we may consider your lack of response as a request to withdraw the ANDA under 21 CFR 314.110(c)(1). You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter does not fulfill the requirements in 21 CFR 314.110(b)(1) and therefore will not be processed as a resubmission and will not start a new review cycle.

The drug product may not be marketed without final Agency approval under section 505(j) of the FD&C Act.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions¹ with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that

it will be a violation of federal law to ship these products in interstate commerce or import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self-identification or fee payment.

GDUFA II provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including by fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the RLD that occur after submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure you stay up to date with the Agency's current thinking on topics through guidances for industry, including product-specific guidances.

If you have any questions, call Gwendolyn Murphy, Regulatory Project Manager, Division of Project Management, at (240) 402 - 9624.

Sincerely yours,

{See appended electronic signature page}

For Denise P. Toyer McKan, PharmD
Director, Division of Project Management
Office of Regulatory Operations
Office of Generic Drugs

¹ Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).



Scott (David)
Vehovic

Digitally signed by Scott (David) Vehovic
Date: 7/09/2020 12:52:50PM
GUID: 508da6fe000285204a945354e421a90b



ANDA 213719

AMENDMENT ACKNOWLEDGEMENT
Priority
Minor

Zydus Pharmaceuticals (USA) Inc.
73-B, Route 31 North
Pennington, NJ 08534
Attention: Srinivas Gurram
VP & Head of RA & QA - North America

Dear Sir:

This is in reference to your amendment received on April 16, 2020, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Sacubitril and Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg.

This amendment is subject to the provisions of the Generic Drug User Fee Amendments of 2017 (GDUFA II). FDA has made an initial determination that this is a minor amendment and it meets the criteria for a priority review per the Center for Drug Evaluation and Research's Manual of Policies and Procedures 5240.3, *Prioritization of the Review of Original ANDAs, Amendments, and Supplements*. The GDUFA goal date for review of this priority minor amendment is July 15, 2020.

GDUFA II provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the RLD that occur after the submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure your application stays up to date with the Agency's current recommendations on demonstrating bioequivalence reflected in relevant product specific guidances.

If you have any questions, contact Gwendolyn Murphy, Regulatory Project Manager, at (240) 402 - 9624.

Sincerely,

{See appended electronic signature page}

Gwendolyn Murphy
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration



Gwendolyn
Murphy

Digitally signed by Gwendolyn Murphy

Date: 4/16/2020 01:47:13PM

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ANDA 213719

AMENDMENT ACKNOWLEDGEMENT
Priority
Major

Zydus Pharmaceuticals (USA) Inc.
73-B, Route 31 North
Pennington, NJ 08534
Attention: Srinivas Gurram
Vice President & Head of RA and QA- North America

Dear Sir:

This is in reference to an amendment to the Drug Master File (DMF) #33452 received on November 23, 2019, 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 major amendment and it meets the criteria for a priority review per the Center for Drug Evaluation and Research's Manual of Policies and Procedures 5240.3, *Prioritization of the Review of Original ANDAs, Amendments, and Supplements*. If FDA determines that an inspection is not required to validate the information contained in this priority major amendment, the GDUFA goal date for review of this priority major amendment is May 22, 2020. If FDA determines that an inspection is required to validate the information contained in this priority major amendment and a Pre-Submission Facility Correspondence was not submitted or not accepted, the GDUFA goal date for review of this priority major amendment is September 22, 2020.

GDUFA II provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the RLD that occur after the submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure your application stays up to date with the Agency's current recommendations on demonstrating bioequivalence reflected in relevant product specific guidances.

If you have any questions, contact Gwendolyn Murphy, Regulatory Project Manager, at (240) 402 - 9624.

Sincerely,

{See appended electronic signature page}

Gwendolyn Murphy
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration



Gwendolyn
Murphy

Digitally signed by Gwendolyn Murphy

Date: 3/10/2020 02:09:08PM

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ANDA 213719

**DISCIPLINE REVIEW LETTER
QUALITY**

Zydus Pharmaceuticals (USA) Inc.
73-B Route 31 North
Pennington, NJ 08534
Attention: Srinivas Gurram

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/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 Deficiencies

1.

2.

(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.

6.

(b)(4)

7.

C. Manufacturing Deficiencies

Process

1.

(b)(4)

2.

3.

Facility

1.

(b)(4)

(b)(4)

D. Biopharmaceutics Deficiencies

1. The proposed dissolution method (b)(4) is not acceptable at this stage because:

(b)(4)

- i)
- ii)
- iii) (b)(4)

The limited data/information provided are not adequate to demonstrate the suitability/discriminating ability of the proposed dissolution method for your proposed drug product. Please note that the discriminating ability of the dissolution method should be investigated towards the critical material attributes (CMAs), critical process parameters (CPPs) and critical formulation variables (CFVs) which affect dissolution. In general, the testing conducted to demonstrate the discriminating ability of the dissolution method should compare the dissolution profiles of the proposed drug product(target) and the formulations/product that are intentionally manufactured with meaningful variations, i.e., aberrant formulations and manufacturing conditions with $\pm 10-20\%$ change to the specification-ranges of these variables for the most relevant CMA's and CPPs. Submit a separate dissolution method development report.

2. The dissolution data demonstrate that the dissolution of some units of the test product remains incomplete using your proposed method, for example some units of Batch #ME80343 dissolved (b)(4) The dissolution profiles of the exhibit batches, including the batch #ME80345, showed (b)(4) (b)(4) In addition, there are differences between the dissolution profiles between the strengths of the proposed drug product. Explain the root cause of the incomplete dissolution and observed high variability of the proposed drug product using your proposed method. Support your explanation with appropriate data.
3. Note that the FDA dissolution database [https://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_SearchResults.cfm] has been updated with a new dissolution method [900 mL of Phosphate Buffer, pH 6.8 using USP apparatus 1 (basket) at 75 rpm]. Please submit dissolution data [(N=12, individual, mean, CV%)] for all your exhibit batches using this new dissolution method. If the dissolution of your proposed drug product remains

(b)(4)

If you choose to follow this new FDA database dissolution method (Basket/75 rpm), then please submit the information/data showing the suitability/discriminating ability of the proposed dissolution method for your proposed drug product, as per above recommendations regarding the demonstration of the suitability/discriminating ability of the method.

If you would like to respond to these possible deficiencies before the end of this review cycle, we request a complete written response to this discipline review letter (DRL) no later than **January 23, 2020**. If you submit a written response during this review cycle, depending on the timing and/or the information contained in your response, we may not be able to consider your response before taking action on your application. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

**DISCIPLINE REVIEW LETTER
QUALITY**

Please note that we are providing these preliminary thoughts on possible deficiencies to you before a complete review of your entire application. As contemplated in the Generic Drug User Fee Amendments of 2017 (GDUFA II) Commitment Letter¹, these possible deficiencies do not reflect a complete review of your application and should not be construed as such. In addition, these possible deficiencies do not necessarily reflect input from supervisory levels. You should be aware that these deficiencies may be modified, or additional deficiencies may be identified as we complete our review of your entire application.

Deficiencies addressed by applicants in a response to a DRL may appear in a Complete Response Letter (CRL) if FDA's review of the response has been deferred or if FDA has outstanding concerns after review of the response. The CRL will include all deficiencies that must be satisfactorily addressed before the ANDA can be approved.

If the applicant receives a CRL but has already responded to some (or all) identified deficiencies in a DRL response, the applicant does not need to re-submit previously submitted information in a CRL amendment. However, the applicant should still submit

¹ GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (available at: <https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf>).

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 Adrienne Belton, Regulatory Business Process Manager, at Adrienne.Belton@fda.hhs.gov or 240-402-4024.

Sincerely,

{See appended electronic signature page}

Adrienne M. Belton, Pharm.D.
Regulatory Business Process Manager
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
U.S. Food and Drug Administration



Adrienne
Belton

Digitally signed by Adrienne Belton
Date: 12/23/2019 02:09:49PM
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ANDA 213719

**DISCIPLINE REVIEW LETTER
BIOEQUIVALENCE**

Zydus Pharmaceuticals (USA) Inc.
73-B, Route 31 North
Pennington, NJ 08534
Attention: Srinivas Gurram
VP & Head of RA & QA - North America

Dear Srinivas Gurram:

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:

Pharmacokinetic (PK) Bioequivalence (BE) Studies

Deficiency Related to Pre-Study Method Validation

1. Please specify what anticoagulant was used in Addendum-I of your method validation AP LC/MS/MS 528.MV.001 (7/8/2019 submission, Module 5.3.1.4 BA17861024-01...\attachment-6-2-addendum-1-method-val-reports).

Deficiency Related to Fasting Study BA18086532

2. The Agency acknowledges that you provided SAS .xpt datasets for subjects that completed all 4 periods of the study (7/8/2019 submission, Module 5.3.1.2. BA18086532...\Data Analysis Data\Analysis Dataset Legacy\pk-sacubitril.xpt, \raw-sacubitril.xpt, \pk-valsartan.xpt, and \raw-valsartan/xpt). Please update your SAS .xpt datasets to also include data from all discontinued subjects (i.e., Subjects

If you would like to respond to these possible deficiencies before the end of this review cycle, we request a complete written response to this discipline review letter (DRL) no later than January 22, 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
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 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 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: 12/22/2019 04:39:42PM
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ANDA 213719

**DISCIPLINE REVIEW LETTER
LABELING**

Zydus Pharmaceuticals (USA) Inc.
73-B, Route 31 North
Pennington, New Jersey 08534
Attention: Srinivas Gurram
VP & Head of RA & QA - North America

Dear Mr. Gurram:

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 2, 2019, based on your submission received July 8, 2019:

1. GENERAL COMMENT- This drug product contains more than 1 active moiety. Use the word "and" in the established name when cross reference to "Entresto" is made in the reference listed drug labeling. i.e. "sacubitril and valsartan tablets". We recommend this change to your labels principal display panel and in the insert/patient leaflet labeling. Use title case letter in the product name when appropriate.
2. CONTAINER LABELS
 - a. Revise the expression of strength statement by deleting the extra spaces (eq., XX mg/XX mg rather than XX mg / XX mg)
 - b. Relocate the net quantity statement to the bottom portion of the label or top portion near the NDC numbers to ensure this statement is not near the declaration of strength statement.
3. BLISTER LABELS, please note comment under CONTAINER LABELS (2.a.) above, regarding the extra space in the strength statement.
4. UNIT DOSE CARTONS

a.

(b)(4)

b. Please refer to CONTAINER LABELS, comment (a) and revise cartons accordingly.

5. 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. BLACK BOXED WARNING, revise to read "...discontinue sacubitril and valsartan tablets as soon..." (b)(4)
- d. Throughout the labeling and especially in the INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, DESCRIPTION, and HOW SUPPLIED sections, please ensure "tablets" is part of the established name wherever "Entresto" is cited in the reference listed drug insert labeling.
- e. DESCRIPTION section declare "tartrazine" in association with FD&C yellow #5 in the description section.
- f. WARNING AND PRECAUTIONS

The 97 mg/103 mg strength tablets contain FD&C Yellow # 5 (tartrazine) aluminum lake. Include the required warning statement to appear as the last subsection in the WARNINGS AND PRECAUTIONS section of the labeling titled "5.X Risk of Allergic Reactions Due to Tartrazine", in accordance with 21 CFR 201.20 (b). Additionally, include the subsection number in the FULL PRESCRIBING INFORMATION: CONTENTS*.

6. PATIENT INFORMATION

a. See comments under professional labeling regarding updates to the RLD labeling.

b.

(b)(4)

- c. In the **“What are the ingredients in sacubitril and valsartan tablets?” section**, in the second inactive ingredient paragraph, declare the presence of tartrazine no. 5 in association with FD&C yellow #5 Aluminum Lake.

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 December 02, 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

¹ GDUFA II Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (available at: <https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf>).

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.

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: 11/15/2019 10:58:54AM
GUID: 5508755d000926ebceca6d5de2d276c5



ANDA 213719

**PARAGRAPH IV ACKNOWLEDGEMENT
ANDA RECEIPT**

Zydus Pharmaceuticals (USA) Inc.
73-B, Route 31 North
Pennington, NJ 08534
Attention: Srinivas Gurram (Srini)

Dear Srinivas Gurram (Srini):

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 Gwendolyn Murphy, Regulatory Project Manager, at gwendolyn.murphy@fda.hhs.gov¹ or (240) 402 - 9624. 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}

Annie Phung, 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>



Annie
Phung

Digitally signed by Annie Phung

Date: 8/30/2019 07:37:13AM

GUID: 5582f75300341b8c8b0a95a6e4124878

List of Deficiencies for DRL

A. Overall Quality Deficiencies - Optional (Deficiencies that affect multiple sub-disciplines)

B. Drug Substance Deficiencies

- 1.
 - 2.
- (b)(4)**

C. Drug Product Deficiencies

- 1.
 - 2.
- (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.

7.

(b)(4)

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

None.

E. Manufacturing Deficiencies

1.

2.

3.

4.

(b)(4)

F. Biopharmaceutics Deficiencies

1. The proposed dissolution method

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Please note that the discriminating ability of the dissolution method should be investigated towards the critical material attributes (CMAs), critical process parameters (CPPs) and critical formulation variables (CFVs) which affect dissolution. In general, the testing conducted to demonstrate the discriminating ability of the dissolution method should compare the dissolution profiles of the proposed drug product(target) and the formulations/product that are intentionally manufactured with meaningful variations, i.e., aberrant formulations and manufacturing conditions with $\pm$ 10-20% change to the specification-ranges of these variables for the most relevant CMA's and CPPs. Submit a separate dissolution method development report.

2. The dissolution data demonstrate that the dissolution of some units of the test product remains incomplete using your proposed method, for example some units of Batch #ME80343

(b)(4) The dissolution profiles of the exhibit batches, including the batch #ME80345, showed

(b)(4) In addition, there are differences between the dissolution profiles between the strengths of the proposed drug product. Explain the root cause of the incomplete dissolution and observed high variability of the proposed drug product using your proposed method. Support your explanation with appropriate data.

3. Note that the FDA dissolution database [https://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_SearchResults.cfm] has been updated with a new dissolution method [900 mL of Phosphate Buffer, pH 6.8 using USP apparatus 1 (basket) at 75 rpm]. Please submit dissolution data [(N=12, individual, mean, CV%)] for all your exhibits batches using this new dissolution method. If the dissolution of your proposed drug product remains incomplete or you notice cone formation using the originally proposed dissolution method (b)(4), then you may consider this new FDA database dissolution method (Basket/75 rpm) for the quality control testing of your proposed drug product. If you choose to follow this new FDA database dissolution method (Basket/75 rpm), then please submit the information/data showing the suitability/discriminating ability of the proposed dissolution method for your proposed drug product, as per above recommendations regarding the demonstration of the suitability/discriminating ability of the method.

G. Microbiology Deficiencies

H. Other Deficiencies (Specify discipline, such as Environmental)

Application Technical Lead Name and Date: