CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218591Orig1s000, 207620Orig1s025

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	218591
Applicant Name	Novartis Pharmaceuticals Corporation
Drug Product Name	ENTRESTO® Sprinkle (sacubitril and valsartan)
Dosage Form.	Oral Pellets
Proposed Strength(s)	6 mg sacubitril/6 mg valsartan; 15 mg sacubitril/16 mg valsartan
Route of Administration	Oral
Maximum Daily Dose	97 mg sacubitril/ 103 mg valsartan
Rx/OTC Dispensed	Rx
Proposed Indication	• to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure. Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal. (1.1) • 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. (1.2)
Drug Product Description	• ENTRESTO 6 mg/6 mg, (sacubitril 6 mg and valsartan 6 mg) consists of a white colored cap with “04” and a transparent body with “NVR” and both parts with arrows. • ENTRESTO 15 mg/16 mg, (sacubitril 15 mg and valsartan 16 mg) consists of a yellow colored cap with “10” and a transparent body with “NVR” and both parts with arrows.
Co-packaged product information	N/A
Device information:	N/A

Storage Temperature/ Conditions	20 °C to 25 °C		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Zhengfu Wang	N/A
	Drug Product/ Labeling	Akm Khairuzzaman	Theodore Carver
	Manufacturing	Liya Tang	Feiyan Jin
	Biopharmaceutics	Parnali Chatterjee	Haritha Mandula
	Microbiology	N/A	
	Other (specify):	N/A	
	RBPM	Grafton Adams	
	ATL	Theodore Carver	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating:

A shelf life of 36 months is granted for the drug product when stored at 20°C to 25°C.

b. Additional Comments for Action
None.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

1. Background

The proposed 505(b)(1) NDA application is for ENTRESTO® Sprinkle (sacubitril/valsartan) oral film-coated granules/ 6 mg/6 mg and 15mg/16 mg. This new product is an extension of the Applicant's currently marketed product, ENTRESTO® (sacubitril and valsartan) tablets, 24/26 mg; 49/51 mg; 97/103 mg. This product is for pediatric patient population and patients unable to swallow the tablet formulation. It is also intended to replace, where feasible, the preparation of suspensions from the currently marketed tablet formulation. This NDA is being reviewed in parallel with the supplemental NDA 207620 (Sequence 25), and the changes to the Entresto labeling and corresponding clinical review are included in that sNDA.

2. Drug substance (sacubitril/valsartan sodium hydrate)

The drug substance, LCZ696-(b) (4) is a salt complex comprising the anionic molecular moieties of sacubitril and valsartan, sodium cations and water molecules in the molar ratio of 1:1:3:2.5. Drug substance information is cross-referenced to the active NDA 207620, and all information was found to be adequate to support this NDA.

3. Drug Product (sacubitril and valsartan oral pellets)

The drug product comprises immediate oral pellets manufactured as minitablets (described as granules in Module 3 of the NDA) (b) (4) and packaged in hypromellose capsules. Each pellet or minitablet contains 1.518 mg/1.607 mg sacubitril/valsartan, and there are four pellets per capsule for the lower strength drug product (6 mg/6mg) and 10 pellets per capsule for the higher strength drug product (15mg/16mg). The drug product is administered by sprinkling on soft foods (b) (4), the capsules are never to be taken whole, as indicated in the dosing instructions in the labeling and medication guide. All excipients are compendial and adequate batch and stability data were provided for review. Food compatibility studies were provided to support the dosing instructions for sprinkling on specified soft foods (b) (4) The review concluded that the drug product information is acceptable and that a shelf life of 36 months (extrapolated from 24 months real-time stability data) can be granted for the drug product stored at 20ºC to 25ºC.

4. Manufacturing

Process - The film-coated oral pellets (described as granules in Module 3) are manufactured (b) (4) The process information was found to be adequate.

Facilities – A pre-approval inspection (PAI) of the drug product manufacturing facility, Novartis d.o.o. in Verovskova Ulica 57, Ljubljana, 1000, Slovenia, 1526 (FEI: 3013358397) was conducted with a final recommendation for this facility of approval based on the Initial Field Recommendation provided by ORA and OPMA for this PAI. All other facilities were approved based on their previous inspection history. Therefore, the overall recommendation for facilities is approval.

5. Biopharmaceutics

The biopharmaceutics review concluded that the formulation bridging and dissolution test method information are adequate to support approval. Based on a final conclusion of 'medium' risk with respect to dissolution, correct administration of the dosage form by sprinkling is a requirement of the formulation (swallowing capsules whole is not supported).

6. Quality Labeling

The quality labeling review concluded that the labeling is adequate except for the proposed dosage form of granules, which was recommended to be changed to capsules in the primary labeling review and conclusion below. However, the secondary reviewer and ATL, in consultation with the OPQ labeling working group and labeling experts, agreed with the final dosage form of "oral pellets". Because the capsules shells serve as a container for the drug product and are not to be administered to the patient, use of the dosage form "capsule" is inappropriate for drug products administered only by sprinkling onto foods (b) (4). In addition, the dosage form initially proposed by the Applicant, "granules", is also inappropriate, because, as described in USP <1151>, "granules" is intended to describe particles that are irregular in shape, as opposed to the minitablet in the ENTRESTO® Sprinkle formulation, which are very regular in shape, consistent with the description of pellets in USP <1151>. In response to an information request, the Applicant agreed to change the dosage form to "oral pellets." Therefore, the labeling is now concluded to be adequate to support approval of NDA 218591, with the changes agreed to by the Applicant to be finalized in final labeling discussions. See also DMEPA review with regards to product dosing instructions and naming to minimize risk of patients swallowing capsules whole.

b. Is the overall recommendation in agreement with the individual discipline recommendations? No

All subdisciplines concluded that the information submitted to the NDA is adequate to support approval except for quality labeling. The primary quality labeling reviewer concluded that the proposed final dosage form of "oral

pellets" is inadequate, and the reviewer was unwilling to change his conclusion after further team discussions. This conclusion was changed to "adequate" by the secondary reviewer and ATL in consultation with the Office of Pharmaceutical Quality Labeling Working Group and OPQ expert reviewers. See summary of quality labeling review above. The final review conclusion of the Integrated Quality Assessment for all subdisciplines, including quality labeling, is "adequate."

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Inadequate***
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**Adequate**
Microbiology	**-**	**N/A**

*changed to "Adequate" in the final review, see above.

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:
None.

Comparability Protocols (PACMP): No
Comments:
None.

Additional Lifecycle Comments:

1. The drug product includes minitablets inside a capsule shell. The manufacturing of the minitablets is a fairly complex process. Any change in the mini tablet (b) (4) process may need a prior approval supplement.

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Theodore Carver

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CHAPTER IV: LABELING

For more details about the items in this template, please see Chapter IV (Labeling) of the NDA IQA Guide

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights		
Established name(s)[1]	Inadequate	Proposed name: ENTRESTO® (sacubitril and valsartan) (b) (4) In response to an CMC IR, on 12/08/2023, the Applicant agreed to revise the name as ***Entresto Sprinkle ® (sacubitril and valsartan)*** (b) (4) The proposed name is not consistent the current FDA's dosage form database as well as the USP chapter 1151. Most of the FDA approved products like this that are either dosed as is or sprinkled on soft food are called as "Capsule". However, although this product is meant to be sprinkled only, but it is supplied as capsule in a bottle. Since the product presentation includes a capsule and the content is meant to be sprinkled with the soft food, the product name should be: ***ENTRESTO Sprinkle (sacubitril/valsartan) capsules,*** (b) (4) *This has been further consulted with the OPQ-ONDP-Labeling group. For final decision, I defer this to the dosage form nomenclature group and my secondary reviewer.*
Route(s) of administration	Adequate	Oral

[1] Established name = [Drug] [Route of Administration] [Dosage Form]

Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	6 mg/6 mg; 15 mg/16 mg
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state “functionally scored”.	N/A	Not a tablet
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	Not an injectable product
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).	Adequate	Strength is based on the active moiety

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Adequate	Under section 2.5, the following instruction is provided: "To administer ENTRESTO (b) (4) open the capsule and sprinkle the full content onto 1 to 2 teaspoons of soft food. Consume the food containing the (b) (4) immediately after adding them. (b) (4) (b) (4) empty capsule shells must be discarded after use and not swallowed." **The following revision is required**: "ENTRESTO (b) (4) need to be replaced with " ENTRESTO SPRINKLE capsules"
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	Adequate	Section 2.5 instructs not to swallow the capsule (see above).
For parenteral products: include statement: *"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"*	N/A	Not a parenteral product.

If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	There is no USP monograph.
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	Not a radioactive product.
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]"* with x numerical citation to "OSHA Hazardous Drugs".	N/A	Not applicable.

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Inadequate	Section 3 describes the product as a "film coated (b) (4). The Sprinkles are mini tablets that are supplied in a capsule. Therefore the dosage form should be described as "capsule"
Strength(s) in metric system	Adequate	ENTRESTO 6 mg/6 mg, (sacubitril 6 mg and valsartan 6 mg) ENTRESTO 15 mg/16 mg, (sacubitril 15 mg and valsartan 16 mg)
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).	Adequate	the strengths are based on the active moiety

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Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	Inadequate	ENTRESTO film-coated (b) (4) are (b) (4) in a hard capsule in the following strengths: • ENTRESTO 6 mg/6 mg, (sacubitril 6 mg and valsartan 6 mg) consists of a white colored cap with "04" and a transparent body with "NVR" and both parts with arrows. • ENTRESTO 15 mg/16 mg, (sacubitril 15 mg and valsartan 16 mg) consists of a yellow colored cap with "10" and a transparent body with "NVR" and both parts with arrows **Should read as:** ENTRESTO ~~film-coated~~ (b) (4) SPRINKLE capsules are (b) (4) hard capsule in the following strengths: • ENTRESTO 6 mg/6 mg, (sacubitril 6 mg and valsartan 6 mg) consists of a white colored cap with "04" and a transparent body with "NVR" and both parts with arrows. • ENTRESTO 15 mg/16 mg, (sacubitril 15 mg and valsartan 16 mg) consists of a yellow colored cap with "10" and a transparent body with "NVR" and both parts with arrows
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	Not a tablet dosage form
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	Not an injectable product.

Section 11 (DESCRIPTION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)	Inadequate	Section 11 says, " ENTRESTO is available as film-coated (b) (4) for oral administration" **Should read as** " ENTRESTO Capsules contain (b) (4) for oral administration"
Dosage form(s) and route(s) of administration	Inadequate	Section 11 says, " ENTRESTO is available as film-coated (b) (4) for oral administration" **Should read as** " ENTRESTO Capsules contain (b) (4) for oral administration"
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	N/A	There is no USP monograph.
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Adequate	Provided in alphabetical order under section 11
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	Not a parenteral injectable dosage form.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	There is no alcohol in the formulation.
Sterility statement (if applicable)	N/A	Not a sterile product.

Pharmacological/Therapeutic class	Inadequate	Provided under section 11 as *"ENTRESTO (sacubitril and valsartan) is a combination of a neprilysin inhibitor and an ARB."* ***Should read as:*** "*ENTRESTO (sacubitril and valsartan) is a combination of a neprilysin inhibitor and an angiotensin eceptor Blocker (ARB)"*
Chemical name, structural formula, molecular weight	Adequate	Provided under section 11, page 11-12.
If radioactive, statement of important nuclear characteristics.	N/A	Not a radioactive compound.
Other important chemical or physical properties (such as pKa or pH)	Adequate	provided under section 11.
For oral prescription drug products, include gluten statement (if applicable)	N/A	None
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	N/A	None
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	There is no USP monograph.

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

APPEARS THIS WAY ON ORIGINAL

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	Sections 16 says, "ENTRESTO film-coated (b) (4) are round, biconvex in shape. (b) (4) (b) (4) (b) (4) provided in a hard capsule (b) (4) (b) (4)
Strength(s) in metric system	Adequate	6 mg/6 mg and 15 mg/16 mg
Available units (e.g., bottles of 100 tablets)	Adequate	packaged in bottles of 60
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	Adequately provided for each strength under the section 16 as follows. (b) (4)
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	Not a tablet
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	Not an injectable product.

Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs."	Inadequate	Section 16 should include the following statements: ***"Do NOT swallow the whole capsule"*** ***"Do NOT swallow the empty capsule shells"***

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	The following statements are provided. "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."
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*	N/A	There is no "latex-free" statement in the labeling.
Include information about child-resistant packaging	Adequate	(b) (4)

1.2.5 Other Sections of Labeling

There is no other sections of labeling that contain product-quality related information such as warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenteral, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol].

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Adequate	Container labeling has the following information: Distributed by: Novartis Pharmaceuticals Corporation East Hanover, New Jersey 07936.

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides, Instructions for Use, Patient Information):

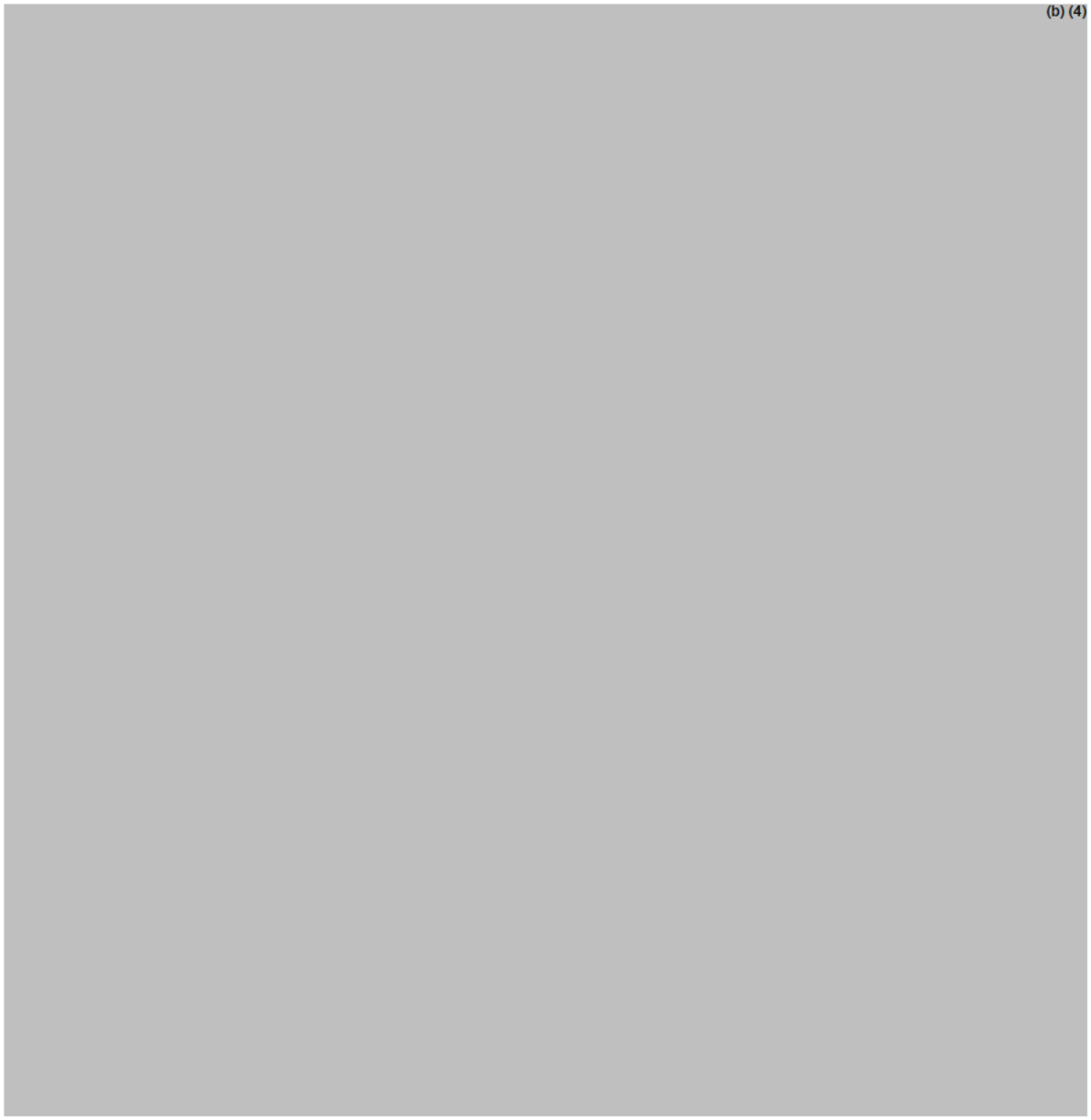
Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Medication Guide (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[2]	Inadequate	ENTRESTO should be followed by Sprinkle or another appropriate modifier
Special preparation instructions (if applicable)	Adequate	The following statement is provided: "The capsules (b) (4) must be opened (b) (4) • Do NOT swallow the (b) (4) capsule. • (b) (4) the empty capsule shells." A detailed step-by-step instruction along with pictures is provided on how to open the capsule shell and mix the sprinkles with soft food prior to administration.
Storage and handling information (if applicable)	Adequate	Provided
Active ingredient(s) (if applicable)	Adequate	Provided
Alphabetical listing of inactive ingredients (if applicable)	Adequate	Provided

[2] Established name = [Drug] [Route of Administration] [Dosage Form]

3.0 CONTAINER AND CARTON LABELING

3.1 Container Labels

(b) (4)



3.2 Carton Labeling

There is no carton

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Container Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[3], (font size and prominence)	Inadequate	Proposed name: ENTRESTO® (sacubitril and valsartan) (b) (4) CMC Reviewer recommends: ***ENTRESTO Sprinkle (sacubitril/valsartan) capsules,*** (b) (4)
Strength(s) in metric system	Inadequate	Container label says: (b) (4) But the dosage form and strength on the PI says: "6 mg/6 mg; 15 mg/16 mg" Container labels need to be revised to be consistent with PI
Route(s) of administration	Adequate	For oral use
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	Adequate	Currently the approved product container labels for Entresto does not include any equivalence statement
Net contents (e.g., tablet count, volume of liquid)	Adequate	Provided (60 capsules)
"Rx only" displayed on the principal display	Adequate	Provided
NDC	Adequate	Provided
Lot number and expiration date	Adequate	Provided
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	Provided as follows: "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."
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differs from the dosage form.	N/A	None

[3] Established name = [Drug] [Route of Administration] [Dosage Form]

For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement.	N/A	Not a parenteral product
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	Not a parenteral product
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	
Name of manufacturer/distributor /packer	Adequate	Mfd. by: (b) (4) Ljubljana (b) (4) Slovenia Dist. by: Novartis Pharmaceuticals Corp. East Hanover, NJ 07936
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available.	N/A	

Assessment of Carton and Container Labeling: *{Inadequate}*

I recommend that the dosage form nomenclature should be a "Capsule" instead of (b) (4) *However, I defer this to my Team Lead and OPQ's dosage form*

nomenclature committee regarding the dosage form designation for this product: "Capsule" vs. (b) (4)

Applicant should be informed to change their container labeling as follows:

1. Change your container label as follows.
   (a) Strengths: Change from (b) (4) to "6 mg/6 mg; 15 mg/16 mg" to be consistent with the PI.
   (b) Change the product name to "***ENTRESTO Sprinkle* (sacubitril/valsartan) *Capsules,*** (b) (4) ***I also defer this to the Dosage form nomenclature expert group)***
   (c) Include a cautionary statement, "The capsule must not be swallowed."

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation:

Inadequate

Primary Labeling Assessor Name and Date: Akm Khairuzzaman, Ph.D. 2/06/2024

Secondary Assessor Name and Date (and Secondary Summary, as needed): Theodore Carver, Ph.D., 02/06/2024

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Theodore Carver

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Office of Pharmaceutical Quality

New Drug Application (NDA)

Integrated Quality Assessment Template

CHAPTER VI: BIOPHARMACEUTICS

For more details about the items in this template, please see Chapter VI (Biopharmaceutics) of the NDA IQA Guide

Product Information	Immediate-release film-coated granules dispensed in hypromellose capsule
NDA Number	218591
Assessment Cycle Number	ORIG-1
Drug Product Name/ Strength	Entresto® (sacubitril/valsartan) 12.5 mg (6.1 mg/6.4 mg), 31.25 mg (15.18 mg/16.07 mg) film-coated granules
Route of Administration	Oral
Applicant Name	Novartis Pharmaceuticals Corporation
Therapeutic Classification/ OND Division	OCHEN/DCN
Proposed Indication	For treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older

Assessment Recommendation: **Adequate**

Assessment Summary:

In this NDA submission, an immediate-release, fixed-dose combination pediatric formulation, Entresto™ (sacubitril and valsartan, LCZ696 (b) (4)), 12.5 mg strength (6.1 mg/6.4 mg; sacubitril/valsartan) and 31.25 mg strength (15.18 mg/16.07 mg; sacubitril/valsartan) film-coated granules is proposed for the treatment of heart failure in pediatric patients aged one year and older. The recommended dose should be taken orally twice a day and can be adjusted every 2 weeks. Previously, an adult formulation Entresto™ (sacubitril and valsartan, LCZ696 (b) (4) tablets, 24/26 mg; 49/51 mg; 97/103 mg was approved under NDA 207620 on 07/07/2015 for the treatment of heart failure in adults.

The proposed product is comprised of 4 or 10 units of 3.125 mg granules (each granule contains 1.518 mg/1.607 mg; sacubitril/valsartan) that are encapsuled in an hypromellose (HPMC) capsule which functions as a delivery aid. The granules are composed of LCZ696- (b) (4) a low soluble, sodium salt complex (b) (4) of sacubitril/valsartan containing sacubitril, valsartan, sodium and water molecule in 1:1.3:2.5 molar ratio.

The basis for approvability of this NDA is a pivotal safety, efficacy, and pharmacokinetic study CLCZ696B2319 or B2319 (PANORAMA-HF) that was conducted in pediatric patients, 1 month to <18 years with heart failure.

The objective of this assessment is to evaluate the dissolution data provided to support the proposed dissolution method [*USP App (b) (4) (basket) at 50 rpm in 900 mL phosphate buffer, pH 6.8 at 37°C*] and '*Q=(b) (4) in 20 minutes*' as the acceptance criterion for each strength of the drug product.

Proposed Dissolution Method *[USP App (b) (4) (basket) (b) (4) 0 rpm in 900 mL phosphate buffer, pH 6.8 at 37°C]* ***and Acceptance Criterion*** *[Q=(b) (4) in 20 minutes]:* ***Adequate***

LCZ696 (b) (4) demonstrates low solubility in pH 1.2 and acetate buffer, pH 4.5; hence phosphate buffer, pH 6.8 was selected as the dissolution medium for dissolution testing of the proposed product. Dissolution data was provided to support the different testing parameters, such as the apparatus (USP App 1 (b) (4) rotation speed (50 rpm (b) (4)), and medium volume (b) (4). 900 mL) of the dissolution method.

Limited dissolution data was provided to demonstrate discriminating ability of the proposed dissolution method with respect to the effect of (b) (4) that could be rejected by similarity testing (*f2* value) and the proposed dissolution acceptance criterion. Though the effect of (b) (4) could be considered a critical bioavailability attribute that could have an impact on the in vivo performance, the variations (b) (4) evaluated were greater than 50% and were not a meaningful (i.e., +/-10-20%) change in critical formulation variable or process parameter.

Mean dissolution of the clinical and registration batches administered in the pivotal clinical study, B2319 were very rapid ((b) (4)% in 15 minutes) and similar and support the proposed acceptance criterion of 'Q=(b) (4)% in 20 minutes' for valsartan and sacubitril for each strength of the drug product. No downward trend in dissolution is observed for valsartan and sacubitril from the proposed product on long-term stability for up to 24 months.

Considering the overall dissolution data provided for the clinical and registration batches, the proposed dissolution method *[USP App (b) (4) (basket) at 50 rpm in 900 mL phosphate buffer, pH 6.8 at 37°C]* and acceptance criterion *[Q=(b) (4) in 20 minutes]* are adequate for dissolution testing of valsartan and sacubitril from the proposed drug product.

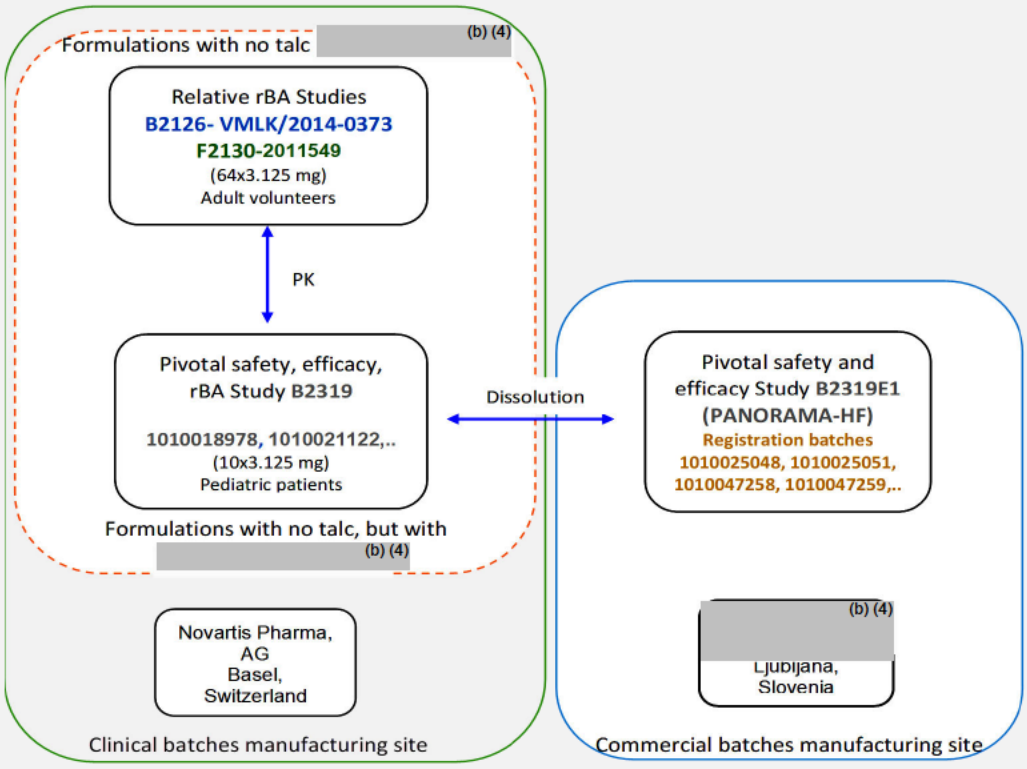
Bridging of Formulations due to Changes (b) (4) and Manufacturing Site: ***Adequate***

The to-be-marketed (TBM), commercial drug product will contain (b) (4) talc (b) (4) However, the clinical batches administered in the pivotal safety, efficacy, and pharmacokinetic study B2319 (PANORAMA-HF) included (b) (4). Moreover, the clinical batches administered in relative bioavailability (rBA) studies, B2126 and F2130 did not include talc (b) (4).

Furthermore, the clinical batches administered in the pivotal safety, efficacy, and pharmacokinetic study B2319 and relative bioavailability (rBA) studies, B2126 and F2130 were manufactured at Novartis Pharma, AG, Basel, Switzerland. The commercial, TBM drug product will be manufactured at (b) (4), Ljubljana, Slovenia.

Dissolution for valsartan and sacubitril from the clinical batches administered in the pivotal safety, efficacy, and pharmacokinetic study B2319 and containing (b) (4) are very rapid (> (b) (4)% in 15 minutes) and similar to the TBM drug product batches containing (b) (4) talc (b) (4). Additionally, the TBM drug product batches are currently administered in the safety and efficacy study, B2319E1.

Based on the totality of the data, the commercial manufacturing site for the TBM drug product containing (b) (4)% talc (b) (4) is 'bridged' through dissolution data, and safety and efficacy study, B2319E1 to the manufacturing site for the clinical batches containing (b) (4).



Recommendation:
Taking into consideration the overall dissolution data, from Biopharmaceutics perspective Entresto® (sacubitril/valsartan), 12.5 mg (6.1 mg/6.4 mg), 31.25 mg (15.18 mg/16.07 mg) film-coated granules is recommended for **APPROVAL**.

The risk of dissolution failures from Biopharmaceutics perspective is considered 'Medium' (see Table below).

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle #1	Comments
Dissolution Method and Acceptance Criterion	Medium	The Biopharmaceutics risk level is medium as the (b) (4) is a low soluble drug substance and limited dissolution data is provided to demonstrate discriminating ability of the proposed dissolution method.	Medium	Biopharmaceutics risk level has been retained at Medium as though dissolution data provided to demonstrate discriminating ability of the proposed dissolution method can differentiate formulations with and without (b) (4) changes in (b) (4) These variations evaluated are either greater than 50% or are not meaningful (i.e., +/- 10-20%) changes in critical material attributes, formulation variables, or process parameters. Other variables evaluated did not have an impact on the dissolution of the variant formulations. As limited dissolution data is provided to support

				the discriminating ability of the proposed dissolution method, the Biopharmaceutics risk level is retained at Medium.

Final Dissolution Method and Acceptance Criterion			
Apparatus	**Rotation Speed (rpm)**	**Medium/ml Temperature (°C)**	**Acceptance Criterion**
USP App 1 (basket)	50 rpm	900 mL phosphate buffer, pH 6.8 at 37℃	Q= (b)(4)% in 20 minutes for Valsartan and Sacubitril

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
Original submission NDA 218591-ORIG-01 (\\CDSESUB1\EVSPROD\nda218591\0000\m1\us\cover.pdf) Pediatric formulation for Entresto® (sacubitril/valsartan) granules	06/14/2023
Original submission NDA 207620-ORIG-01 (\\CDSESUB1\EVSPROD\nda207620\0000\m3\32-body-data\32p-drug-prod\lcz696-film-coated-tablet-01\32p2-pharm-dev\pharmaceutical-development.pdf) Adult formulation for Entresto® (sacubitril/valsartan) tablets approved on 07/07/2015	09/30/2014
Previously approved Post-Marketing Commitment (PMC) for NDA 207620/S005 (\\CDSESUB1\EVSPROD\nda207620\0081\m1\us\cover.pdf) Dissolution method for adult formulation of Entresto® (sacubitril/valsartan) tablets	09/22/2016
Original submission NDA 207620/S013 (\\CDSESUB1\EVSPROD\nda207620\0112\m2\27-clin-sum\synopses-indv-studies-pedshf.pdf) Pediatric safety and efficacy supplement for pediatric formulation of Entresto® (sacubitril/valsartan) granules	04/01/2019
Original submission NDA 207620/S025 \\CDSESUB1\EVSPROD\nda207620\0188\m1\us\cover.pdf Pediatric safety and efficacy supplement for pediatric formulation of Entresto® (sacubitril/valsartan) granules	06/14/2023
IND 104628 (\\CDSESUB1\EVSPROD\ind104628\0829\m1\us\cover.pdf) Pediatric safety and efficacy study for pediatric formulation of Entresto® (sacubitril/valsartan) granules	05/25/2023
Original submission NDA 020665 \\CDSESUB1\EVSPROD\nda020665\0000\m1\us\cover.pdf Adult formulation for Diovan® (valsartan) capsules	12/18/1995
Original submission NDA 021283-S024 https://darrts.fda.gov/darrts/faces/supportingDocument/ Efficacy supplement for Diovan® (valsartan) film-coated tablets	05/29/2007
Original submission NDA 021283-S058 \\CDSESUB1\EVSPROD\nda021283\0110\m1\us\cover.pdf Pediatric efficacy supplement for Diovan® (valsartan) film-coated tablets	06/19/2020

Response to Information Request #1 (\\CDSESUB1\EVSPROD\nda218591\0004\m1\us\cover.pdf)	09/08/2023
Response to Information Request #2 (\\CDSESUB1\EVSPROD\nda218591\0008\m1\us\us-responses-cmc.pdf)	11/16/2023
Response to Information Request #3 (\\CDSESUB1\EVSPROD\nda218591\0012\m1\us\cmc-response-fda.pdf)	12/11/2023

Highlight Key Issues from Last Cycle and Their Resolution: ***Not Applicable***

Key Issues in the Original Submission: Not Applicable

B.1 BCS DESIGNATION

Assessment: BCS IV

In this submission, an immediate-release, pediatric granules formulation is proposed for Entresto™ (sacubitril and valsartan, LCZ696 (b) (4)), 12.5 mg strength (6.1 mg/6.4 mg; sacubitril/valsartan) and 31.25 mg strength (15.18 mg/16.07 mg; sacubitril/valsartan) film-coated granules for the treatment of heart failure in pediatric patients aged one year and older. The recommended dose should be taken orally twice a day as shown in the table below. The dose can be adjusted every 2 weeks.

(b) (4)

Entresto™ (sacubitril and valsartan, LCZ696- (b) (4)) tablets, 24/26 mg; 49/51 mg; 97/103 mg for adult administration was previously approved under NDA 207620 (dated 07/07/2015) for the treatment of heart failure. Under NDA 207620/S005 (dated 09/22/2016), a modified dissolution method [*USP App 1 (basket) at 75 rpm in 900 mL phosphate buffer, pH 6.8 at 37°C*] and acceptance criterion (see **Table 3a**) was approved for dissolution testing of Entresto® (sacubitril/ valsartan) tablets, 24/26 mg; 49/51 mg; 97/103 mg drug product for adult administration.

LCZ696 (b) (4) is a sodium salt complex (b) (4) of sacubitril/valsartan (see **Figure 1**) containing sacubitril, valsartan, sodium and water molecule in 1:1.3:2.5 molar ratio.

There are no official requests for BCS Class I designation for the drug substance or the drug product in the current submission as the sodium complex demonstrates pH-dependent low solubility profile in buffer solutions across the physiological pH range 1.2-6.8. Following oral administration of LCZ696 (b) (4) the complex dissociates rapidly into sacubitril prodrug which further undergoes ester hydrolysis to LBQ657 and valsartan. The absolute bioavailability of sacubitril is low (~60% as LBQ657). However, valsartan demonstrates enhanced bioavailability from the complex.

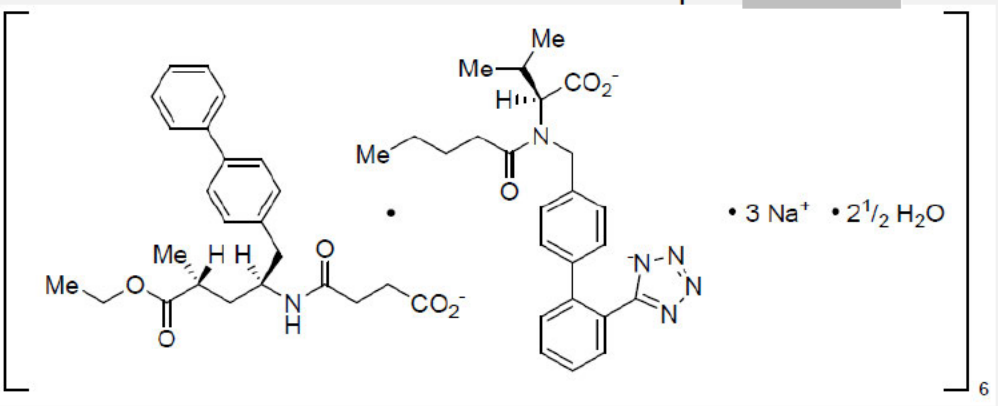
Solubility of the Drug Substance (b) (4)

LCZ696- (b) (4) $C_{48}H_{55}N_6O_8Na_3.2.5H_20$ (as hemipentahydrate)] is a (b) (4) (b) (4) complex of anionic forms of sacubitril and valsartan (b) (4) in chemical coordination with sodium cations and 2.5 water molecules.

(b) (4) LCZ696 (b) (4) contains (b) (4) % water that corresponds to 2.5 molecules of water (referred to as hemipentahydrate) per sacubitril and valsartan molecule.

(b) (4)

Figure 1. Chemical structure of sacubitril and valsartan sodium salt complex (b) (4)



LCZ696 (b) (4) sodium complex demonstrates pH-dependent low solubility profile in buffer solutions across the physiological pH range 1.2-6.8 with low solubility in acidic pH 1.2 (0.1N HCl) and high solubility in water (>100 mg/mL) and phosphate buffer, pH 6.8 (>50 mg/mL) at 25°C (see **Table 1**).

Consequently, the highest dose strength (15.18 mg/16.07 mg; sacubitril/valsartan) of LCZ696 (b) (4) will not be soluble in 250 mL buffer solution across the pH range, 1.2-6.8. Therefore, LCZ696 (b) (4) can be designated as a low soluble drug substance per BCS.

Table 1. Solubility of sacubitril and valsartan sodium salt complex (b) (4) at 25°C

Solvent	Concentration of ARB[1] moiety (mg/ml)	Concentration of NEPi[2] moiety (mg/ml)
0.1N HCl	0.032	0.052
Citrate buffer, pH 3	3.8	0.38
Citrate buffer, pH 5	10.1	1.4
Acetonitrile	1.9	1.9
Acetone	0.28	0.24
Isopropyl acetate	0.007	0.014
Isopropyl alcohol	18.7	18.7
Water	> 100	> 100
Phosphate buffer, pH 6.8	> 50	> 50
Ethanol, absolute	> 50	> 50

[1] ARB – angiotensin receptor blocker (valsartan, VAL489)

[2] NEPi – neutral endopeptidase inhibitor (sacubitril, AHU377)

Permeability of the Drug Substance (b) (4)

As per the Labelling for Entresto™ (sacubitril and valsartan) tablets [NDA 207620, approved on 07/07/2015], following oral administration, LCZ696 (b) (4) dissociates rapidly into sacubitril prodrug (that further undergoes ester hydrolysis to active LBQ657) and valsartan. The time to reach peak plasma concentration (T_{max}) for sacubitril was determined to be 0.5 h, 2 h for LBQ657, and 1.5 h for valsartan, whereas the terminal half-life ($t_{1/2}$) for sacubitril was 1.43 h, 11.48 h for LBQ657, and 9.9 h for valsartan in healthy subjects.

The absolute oral bioavailability of sacubitril from LCZ696 (b) (4) is low (~60% as LBQ657). For valsartan, 400 mg LCZ696- (b) (4) was found to be bioequivalent to 320 mg valsartan commercial product. Following oral administration of ^{14}C-LCZ696 (radiolabeled sacubitril), ~52-68% of total sacubitril dose was recovered as LBQ657 in urine, whereas ~37-48% of total radioactive dose was recovered in feces as LBQ657. Unchanged sacubitril accounted for <3% dose in urine and <1% dose in feces.

The Applicant designated LCZ696 (b) (4) as a medium permeability complex.

Dissolution of the Clinical Batches:

***Drug Products Administered in the Clinical Trials*:**

The proposed product is an immediate-release, fixed-dose combination product composed of 4 or 10 units of 3.125 mg granules (each granule contains 1.518 mg/1.607 mg; sacubitril/valsartan) that are encapsuled in a hypromellose capsule.

Two dose strengths are proposed for the drug product, 12.5 mg strength (6.1 mg/6.4 mg; sacubitril/valsartan) and 31.25 mg strength (15.18 mg/16.07 mg; sacubitril/valsartan) for pediatric administration. The two strengths of the proposed product differ in the number of 3.125 mg (1.518 mg/1.607 mg; sacubitril/valsartan) granules. The 12.5 mg strength drug product is composed of 4×3.125 mg granules, whereas the 31.25 mg strength drug product includes 10×3.125 mg granules in the hypromellose capsule (labeled as granules-in-capsule or GiC in the submission). The capsule functions as a delivery aid for the granules that are intended to be sprinkled over soft food.

The pediatric granule formulation differs from the adult tablet formulation with respect to the absence of (b) (4) crospovidone and (b) (4) the film-coating agent, (b) (4). Additionally, the to-be-marketed (TBM) commercial pediatric formulation includes talc (b) (4)

The granules are manufactured (b) (4) in a hypromellose capsule that is not intended for ingestion.

Comparative composition of the TBM 12.5 mg (6.1 mg/6.4 mg; sacubitril/valsartan) and 31.25 mg (15.18 mg/16.07 mg; sacubitril/valsartan) film-coated granules is provided in **Table 2**.

Table 2. Comparative composition of the TBM 12.5 mg (6.1 mg/6.4 mg; sacubitril/valsartan) and 31.25 mg (15.18 mg/16.07 mg; sacubitril/valsartan) granules

Ingredient	Amount per capsule (mg)		Function	Reference to standards
	12.5 mg[1)]	31.25 mg[2)]		
Granule core				
(b) (4)		(b) (4)	Active ingredient	Novartis specification
(Corresponds to LCZ696 free acid)	(12.5 mg)	(31.25 mg)		
Cellulose, microcrystalline/ Microcrystalline cellulose			(b) (4)	Ph.Eur./ USP/NF
Hydroxypropylcellulose/ Hydroxypropyl cellulose				Ph.Eur./ USP/NF
Magnesium stearate[3)]				Ph.Eur./ USP/NF
(b) (4)				Ph.Eur./ USP/NF
Colloidal silicon dioxide				Ph.Eur./ USP/NF
Talc				Ph.Eur./ USP/NF
Granule core weight		(b) (4)		
Coating			(b) (4)	
Basic butylated methacrylate copolymer				Ph.Eur.
Talc				Ph.Eur./ USP/NF
Stearic acid				Ph.Eur./ USP/NF
(b) (4) Sodium lauryl sulfate				Ph.Eur./ USP/NF
(b) (4)				Ph.Eur./ USP/NF
Film-coated granule weight		(b) (4)		
(b) (4)			(b) (4)	Ph.Eur./ USP/NF
Total film-coated granule weight		(b) (4)		

[1)] LCZ696 12.5 mg corresponds to 6.1 mg of sacubitril and 6.4 mg of valsartan
[2] LCZ696 31.25 mg corresponds to 15.18 mg of sacubitril and 16.07 mg of valsartan
[3)] Vegetable origin
(b) (4)

Drug Products Administered in the Relative Bioavailability (rBA) Studies, B2126 and F2130:

The 3.125 mg (1.518 mg/1.607 mg; sacubitril/valsartan) granules product was administered in the relative bioavailability (rBA) studies, B2126 and F2130, that were conducted in 2014/2015. These clinical batches do not contain talc (b) (4) and are not the final commercial drug product.

Dissolution of the clinical batches administered in the rBA studies, B2126 and F2130 were not provided in the original submission. In an Information Request response (dated 09/08/2023), the Applicant provided dissolution data at 45 minutes for the clinical batch, VMLK/2014-0373 administered in the rBA studies B2126 and clinical batch 2011549 administered in the rBA studies F2130 that demonstrate slower, but > (b) (4)% dissolution of sacubitril and valsartan in 45 minutes (see **Table 3**) using a previously developed dissolution method [*USP App 2 (paddle) at 50 rpm in 900 mL phosphate buffer, pH 6.8 at 37°C*]. Slower dissolution could be due to (b) (4)

Table 3. Dissolution data at 45 minutes for clinical batches, VMLK/2014-0373 and 2011549 administered in the rBA studies B2126 and F2130 using a previously developed dissolution method
[*USP App 2 (paddle) at 50 rpm in 900 mL phosphate buffer, pH 6.8 at 37°C*]

Clinical Batch Number	Relative Bioavailability Study Number	Dissolution Data at 45 minutes	
		Percent (%) Valsartan Released	Percent (%) Sacubitril Released
VMLK/2014-0373	B2126	(b) (4)	(b) (4)
2011549	F2130		

Drug Products Administered in the Pivotal Bioavailability (rBA) Studies, B2319:
Another 12.5 mg (6.1 mg/6.4 mg; sacubitril/valsartan) and 31.25 mg (15.18 mg/16.07 mg; sacubitril/valsartan) film-coated granule product containing (b) (4) (b) (4) was administered in the pivotal safety, efficacy, and pharmacokinetic study B2319. However, this formulation is also not the final commercial drug product.

Comparative dissolution profile data for valsartan and sacubitril were provided for the 12.5 mg and 31.25 mg clinical batches, 1010017611 and 1010018978, respectively, administered in pivotal safety, efficacy, and pharmacokinetic study B2319 that are very rapid (> (b) (4) % in 15 minutes) and similar using the previously developed (paddle) and proposed QC (basket) dissolution method to bridge the two dissolution methods (see **Figure 2a** and **Figure 2b**).

However, these clinical batches contain (b) (4)

Commercial, To-Be-Marketed Drug Product:
The to-be-marketed (TBM) pediatric formulation includes talc (b) (4) In a response to the Information Request (dated 09/08/2023), dissolution profile data (see **Figure 2c** and **Figure 2d**) were provided for the TBM batches to provide a bridge to the clinical batches.

Dissolution of the 12.5 mg and 31.25 mg clinical (containing (b) (4) and registration batches (containing talc) administered in the pivotal clinical study B2319 at release using the proposed QC (basket) dissolution method are rapid (> (b) (4) % in 15 minutes) and similar (no similarity factor, f2 could be calculated as > (b) (4) % dissolved in 10 minutes for some batches).

Considering the overall solubility and permeability data for the drug substance and dissolution data for the clinical and registration batches, LCZ696 (b) (4) could be designated as a BCS Class IV drug substance (b) (4) and the proposed product a BCS Class IV product.

Figure 2a. Comparative dissolution profiles for 12.5 mg clinical batch 1010017611 administered in the pivotal clinical study B2319 at release using the previous (paddle) and proposed QC (basket) dissolution method

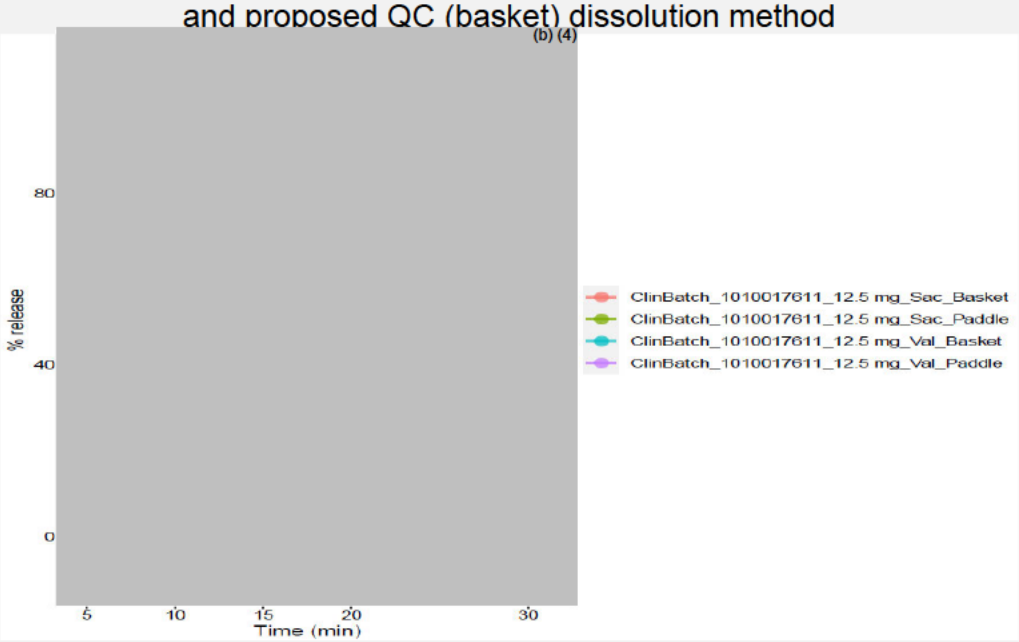


Figure 2b. Comparative dissolution profiles for 31.25 mg clinical batch 1010018978 administered in the pivotal clinical study B2319 at release using the previous (paddle) and proposed QC (basket) dissolution method

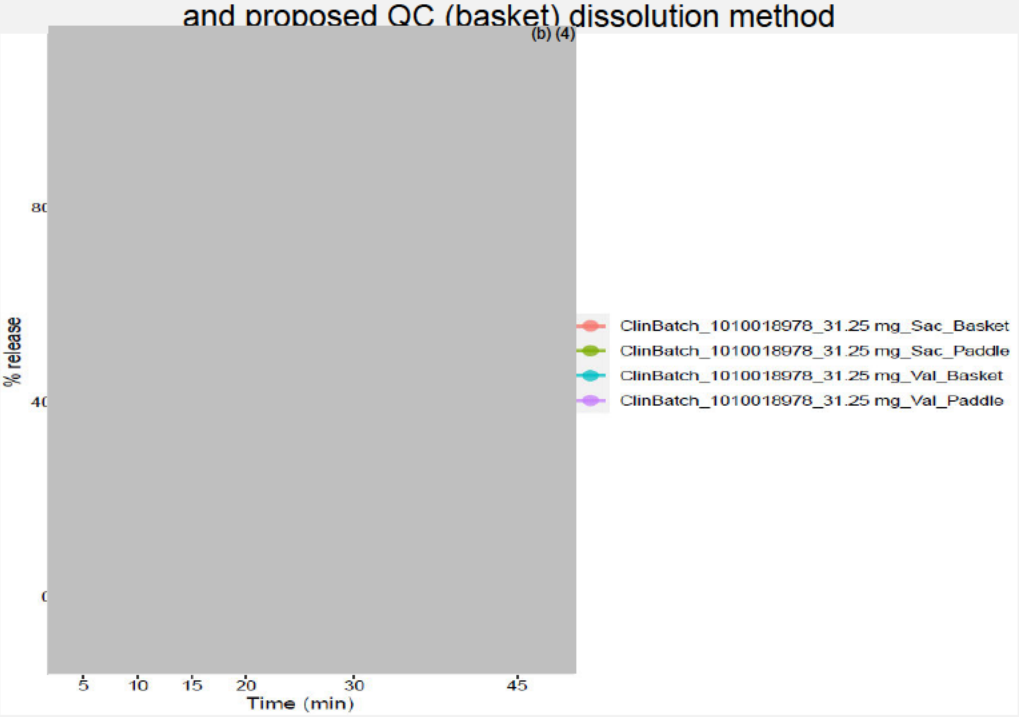


Figure 2c. Comparative dissolution profiles for 12.5 mg clinical (containing (b) (4)) and registration batches (containing talc) administered in the pivotal clinical study B2319 at release using the proposed QC (basket) dissolution method

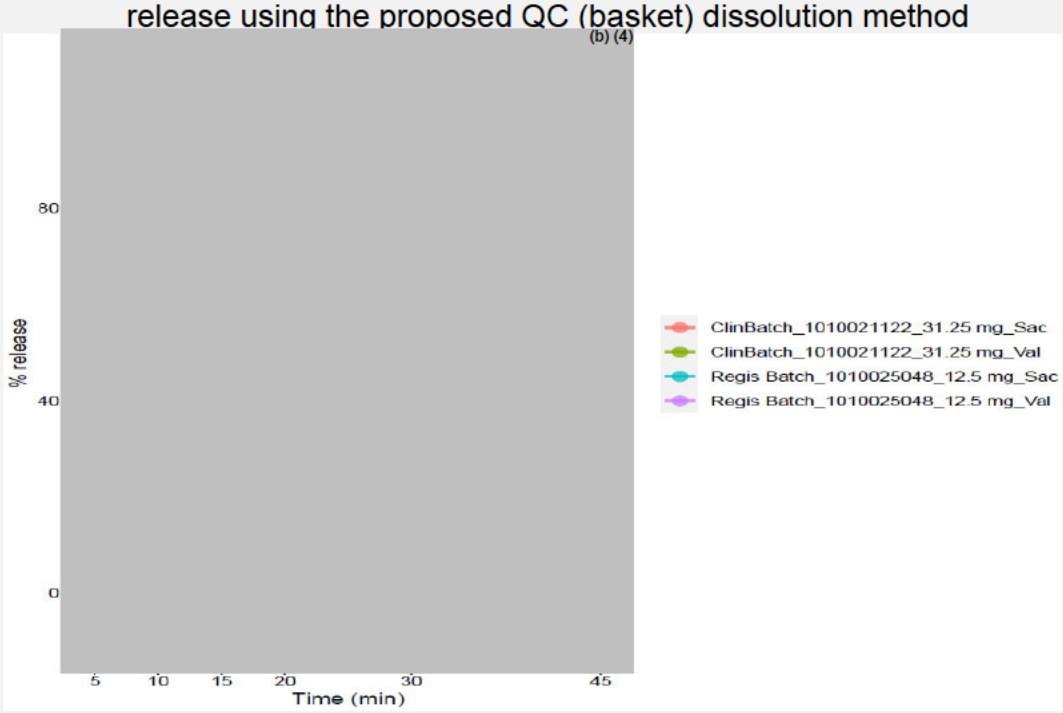
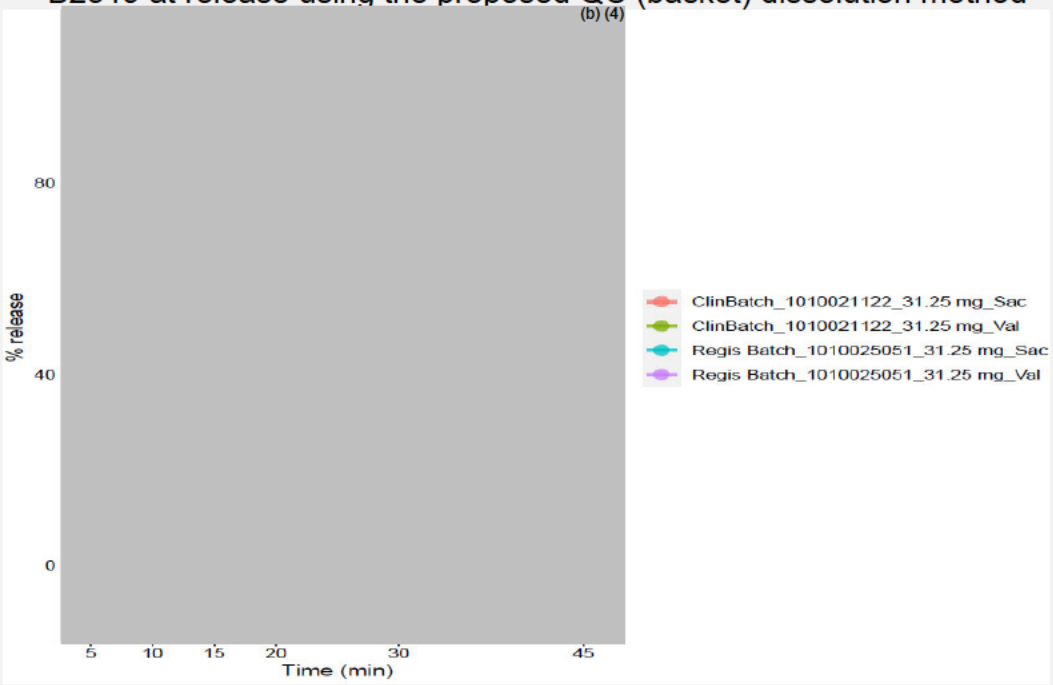


Figure 2d. Comparative dissolution profiles for 31.25 mg clinical (containing (b) (4)) and registration batches (containing (b) (4)) administered in the pivotal clinical study B2319 at release using the proposed QC (basket) dissolution method



B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERION

Assessment: ***{Dissolution Method: Adequate; Acceptance Criterion: Adequate}***

Previously, under NDA 207620/Suppl 005 (dated 09/22/2016), a modified dissolution method [*USP App 1 (basket) at 75 rpm in 900 mL phosphate buffer, pH 6.8 at 37℃*] and acceptance criterion (see **Table 4a**) was approved for dissolution testing of Entresto® (sacubitril/ valsartan) tablets, 24/26 mg; 49/51 mg; 97/103 mg drug product for adult administration.

Table 4a. Previously approved QC dissolution method and acceptance criterion for Entresto®(sacubitril/valsartan) tablets, 24/26 mg; 49/51 mg; 97/103 mg

Approved Dissolution Method and Acceptance Criterion			
Apparatus	**Rotation Speed (rpm)**	**Medium/ml Temperature (°C)**	**Acceptance Criterion Sacubitril/Valsartan**
Apparatus 1 (basket)	75 rpm	900 mL phosphate buffer, pH 6.8 at 37℃	Q= (b)(4)% in 15 minutes for 24/26 mg Q= (b)(4)% in 20 minutes for 49/51 mg Q= (b)(4)% in 30 minutes for 97/103 mg

In the current submission, the Applicant proposed the previously approved dissolution apparatus 1 (basket), dissolution medium (phosphate buffer, pH 6.8 at 37℃), 900 mL medium volume, and a lower (50 rpm) rotation speed (see **Table 4b**) for dissolution testing of Entresto® (sacubitril/valsartan) film-coated granules,12.5 mg (6.1 mg/6.4 mg), 31.25 mg (15.18 mg/16.07 mg) for pediatric administration.

Table 4b. Currently proposed QC dissolution method and acceptance criterion for Entresto® (sacubitril/valsartan) film-coated granules, 12.5 mg (6.1 mg/6.4 mg), 31.25 mg (15.18 mg/16.07 mg)

Proposed Dissolution Method and Acceptance Criterion			
Apparatus	**Rotation Speed (rpm)**	**Medium/ml Temperature (°C)**	**Acceptance Criterion Sacubitril/Valsartan**
Apparatus 1 (basket)	50 rpm	900 mL phosphate buffer, pH 6.8 at 37℃	Q= (b)(4)% in 20 minutes

***Dissolution Method Development for the Proposed QC Dissolution Method*:**

(b) (4)

[redacted]

3 Page(s) have been Withheld in Full as b4 (CCI/ TS) immediately following this page

(b) (4)

[redacted]

Bridging of the Previously and Newly Proposed Dissolution Method:

To establish a 'bridge' between the previously proposed (paddle) and newly proposed QC (basket) dissolution method, comparative dissolution profile data were provided for the 12.5 mg and 31.25 mg clinical batches, 1010017611 and 1010018978, respectively, that were dosed in the pivotal safety, efficacy, and pharmacokinetic study B2319 using the two dissolution methods (see **Figure 3g** and **Figure 3h**).

Dissolution of valsartan and sacubitril from the 12.5 mg (see **Figure 3g)** and 31.25 mg (see **Figure 3h**) clinical batches, 1010017611 and 1010018978, containing (b) (4) [redacted] are very rapid (> (b) (4) [redacted]% in 15 minutes) and similar using the previous (paddle) and proposed QC (basket) dissolution method.

Dissolution of sacubitril and valsartan from other 31.25 mg clinical batch, 1010021122 are rapid (> (b) (4) [redacted]% in 15 minutes) and similar to the 12.5 mg clinical batch, 1010021119 using the proposed QC (basket) dissolution method (see **Figure 3i**).

Reviewers Assessment of the Dissolution Data to Bridge the Dissolution Methods:

Based on the totality of the dissolution profile data provided for the clinical batches administered in the rBA studies B2126 and F2130, and pivotal clinical study B2319, the previous and newly proposed dissolution methods are adequately bridged.

Figure 3g. Comparative dissolution profiles for 12.5 mg clinical batch 1010017611 administered in the pivotal clinical study B2319 at release using the previous (paddle) and proposed QC (basket) dissolution method to bridge the dissolution methods

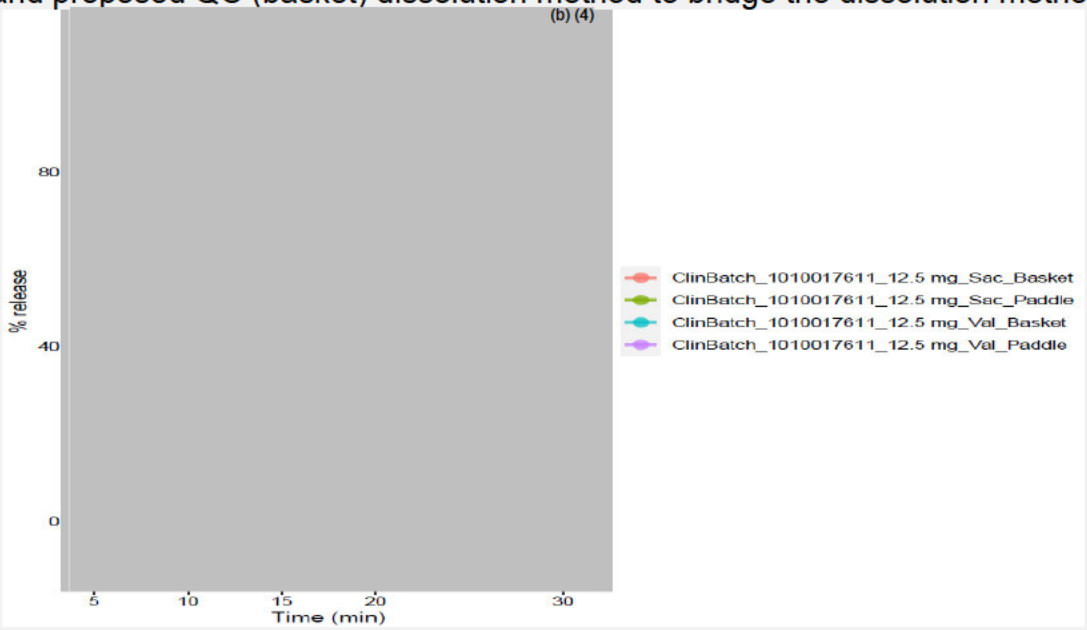


Figure 3h. Comparative dissolution profiles for 31.25 mg clinical batch 1010018978 administered in the pivotal clinical study B2319 at release using the previous (paddle) and proposed QC (basket) dissolution method to bridge the dissolution methods

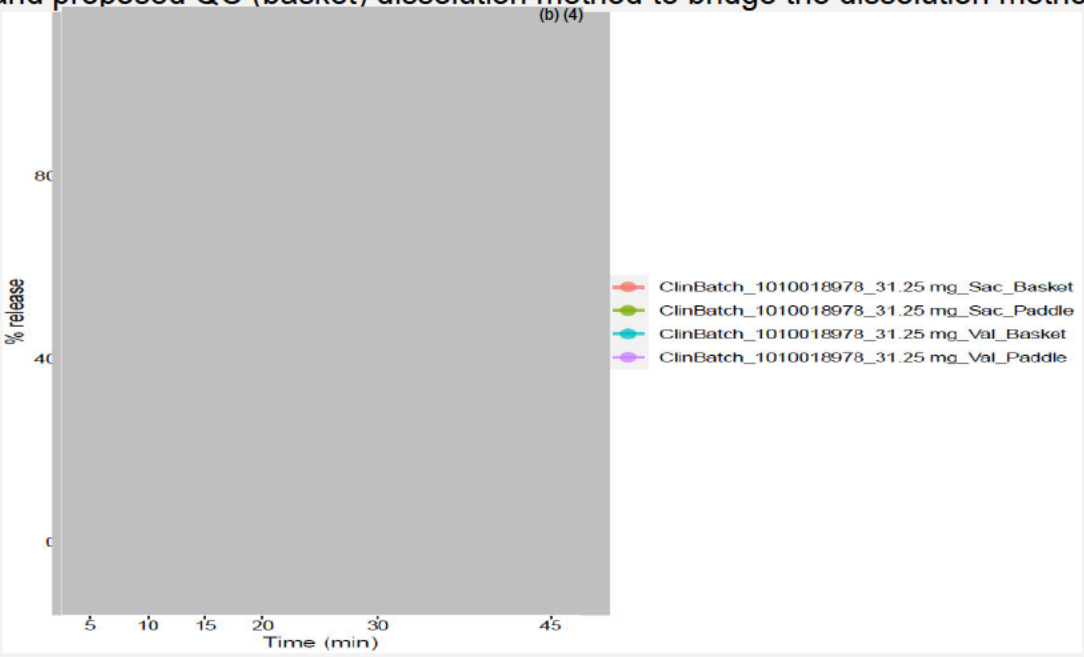
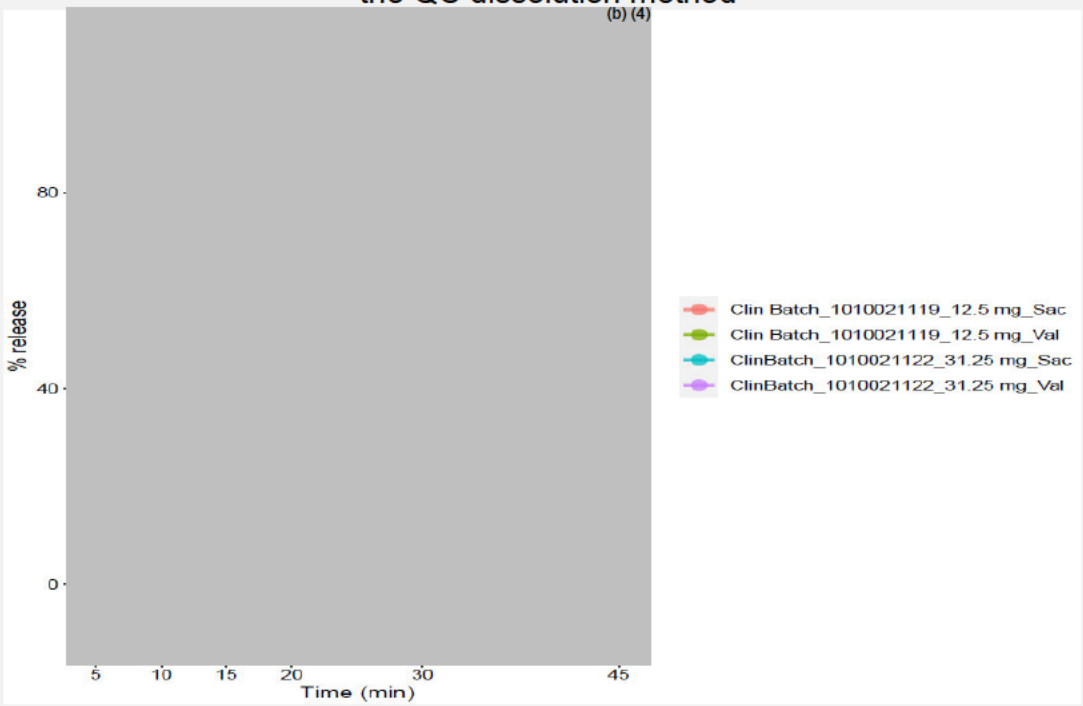


Figure 3i. Comparative dissolution profiles for valsartan and sacubitril from 12.5 mg clinical batch 1010021119 and 31.25 mg clinical batch 1010021122 administered in the pivotal clinical study B2319 at release using the QC dissolution method



Discriminating Ability of the Proposed Dissolution Method:

Manufacturing Process

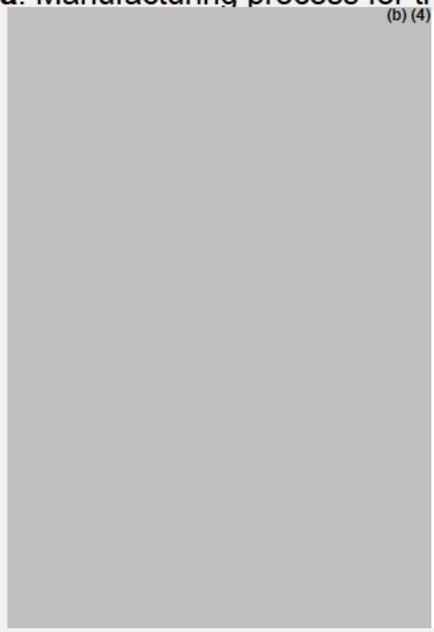
The manufacturing process for the proposed granule product is provided in **Figure 4a**. Briefly, the granules are manufactured (b) (4) and encapsulated in a hypromellose capsule that is not intended for ingestion.

The Applicant identified particle size of the drug complex as a critical material attribute (CMA), (b) (4) as critical process parameters (CPP) that could have an impact on the dissolution of the granule product. In addition, formulation variables (CFVs) such as (b) (4) were identified as critical parameters that could alter the dissolution and in vivo performance of the granule product. The Applicant provided dissolution data for the variant batches with changes in CMAs, CFVs, and CPPs to support the discriminating ability of the proposed dissolution method.

Effect of Material Attribute: Particle size distribution (PSD) of the drug substance. Particle size was identified as a critical material attribute that could have an impact on the dissolution of the drug product (b) (4) however, no dissolution data was provided for drug products containing these drug substance batches.

In addition, numerous drug substance batches were used for manufacturing pre-validation and registration batches of the proposed product at the commercial manufacturing site (see **Table 5**). PSD for the drug substance batches used in the manufacture of the registration batches are very similar, D_{10} (b) (4) µm and D_{90}= (b) (4) µm.

Figure 4a. Manufacturing process for the proposed product



Dissolution of valsartan and sacubitril from 3.125 mg×64 granules from clinical batch, VMLK/2014-0373 administered in the rBA studies B2126 with PSD, D_{90} (b) (4) µm (see **Table 5)** is slower (~ (b) (4)% in 20 minutes) using the proposed dissolution method (see **Figure 4b** and **Figure 4c**). However, the clinical batch contains no talc (b) (4) and 64 granules were used for dissolution testing.

Dissolution of valsartan and sacubitril from other 12.5 mg clinical batches 1010021119 containing (b) (4) administered in the pivotal clinical study B2319 with PSD, D_{10}= (b) (4) µm and D_{90}= (b) (4) µm (see **Table 5)** is very rapid (> (b) (4)% in 15 minutes) and similar to the 12.5 mg registration batch 1010025048 containing talc (b) (4) using the proposed dissolution method (see **Figure 4b** and **Figure 4c**).

Dissolution of valsartan and sacubitril from the registration batches 1010024366, 1010024367 and 1010023713 containing drug substance batches with PSD, D_{10}= (b) (4) µm and D_{90} (b) (4) µm (see **Table 5)** is very rapid (> (b) (4)% in 15 minutes) and similar using the proposed dissolution method.

Based on the overall dissolution data for the clinical batches, no definitive correlation between PSD and dissolution can be established as the clinical batches are considered bioequivalent (see Clinical Pharmacology Review).

The Applicant proposed a two-tier PSD; D_{10} (b) (4) µm and D_{90} (b) (4) µm for the drug substance in the drug product.

Table 5. Particle size distribution for various drug substance batches used in pre-validation and registration drug product batches

DS Batch number	Particle size	Product code Basis/Variant # Global MN	3.125 mg Film-coated granules batch #
C0061 / B492287	D_{10}: (b) (4) µm D_{90}: (b) (4) µm	6003675.007 862135	1010024366 / KA7552
C0061 / B492287	D_{10}: (b) (4) µm D_{90}: (b) (4) µm	6003675.007 862135	1010024367 / KA8122
C0164 / B531040	D_{10}: (b) (4) µm D_{90}: (b) (4) µm	6003675.008 862254	1010023713 / KA8178
B2126 (BA/BE study)	VMLK/2014-0373	C0001/831684	X_{90}: (b) (4) µm
F2130 (BA/BE study)	2011549	C0001/831684	X_{90}: µm
B2319 (Pivotal study)	1010010420	C0002/831899	X_{90}: µm
	1010012663	C0002/831899	X_{90}: µm
	1010015029	C0008/832043	X_{90}: µm
	1010015030	C0008/832043	X_{90}: µm
	1010017611	C0008/832043	X_{90}: µm
	1010021120	C0012/832043	X_{10}: m
			X_{90}: µm
	1010018975	C0012/832043	X_{10}: m
			X_{90}: µm
	1010021119	C0012/832043	X_{10}: m
			X_{90}: µm
Study number	**Batch number**	**Drug substance batch number/ material number**	**Particle size distribution Requirement $X_{90} \leq$ (b) (4) µm***
	1010010421	C0002/831899	X_{90}: (b) (4) µm
	1010012664	C0002/831899	X_{90}: µm
	1010015032	C0008/832043	X_{90}: µm
	1010015031	C0008/832043	X_{90}: µm
	1010017612	C0008/832043	X_{90}: µm
	1010018979	C0012/832043	X_{10}: m
			X_{90}: µm
	1010021124	C0012/832043	X_{10}: m
			X_{90}: µm
	1010021122	C0012/832043	X_{10}: m
			X_{90}: µm

Figure 4b. Comparative dissolution profile for valsartan from clinical batches to support discriminating ability of the proposed dissolution method towards PSD as a material attribute
[USP App 1 (basket) at 50 rpm in 900 mL buffer solution, pH 6.8 at 37°C]

Figure 4c. Dissolution profile data for sacubitril from clinical batches to support discriminating ability of the proposed dissolution method towards PSD as a material attribute
[USP App 1 (basket) at 50 rpm in 900 mL buffer solution, pH 6.8 at 37°C]

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(b) (4)

[redacted]

Reviewer's Assessment of the Discriminating Ability of the Proposed Dissolution Method

Considering the overall dissolution data for the formulation variants, limited dissolution data is provided for valsartan and sacubitril for the variant batches that demonstrate discriminating ability of the proposed dissolution method with respect to the effect of (b) (4) The proposed dissolution method is over-discriminating with respect to the effect of (b) (4) and can reject the dissolution data for valsartan and sacubitril with respect to the similarity test (*f2* value) or the proposed acceptance criterion '*Q=* (b) (4) *% in 20 minutes*'. However, these variations evaluated are greater than 100% and not meaningful (i.e., +/-10-20% change in critical

bioavailability attributes such as material attributes, formulation variables, or process parameters).

Further, none of the other material attributes (API PSD) or process parameters (b) (4) evaluated had an impact on the dissolution of the drug product and were not able to reject the dissolution data for valsartan and sacubitril with respect to the similarity test (*f2* value) or the proposed acceptance criterion '*Q*= (b) (4) *% in 20 minutes*'.

Dissolution Data for Clinical and Registration Batches on Long-Term Stability:

Dissolution data for the clinical batches manufactured at Novartis Pharm, Basel, Switzerland site and registration batches manufactured at the commercial manufacturing site, (b) (4) Ljubljana, Slovenia on long-term and in-use stability conditions do not demonstrate any downward trend and will meet the proposed acceptance criterion '*Q*= (b) (4) *% in 20 minutes*' for up to 24 months.

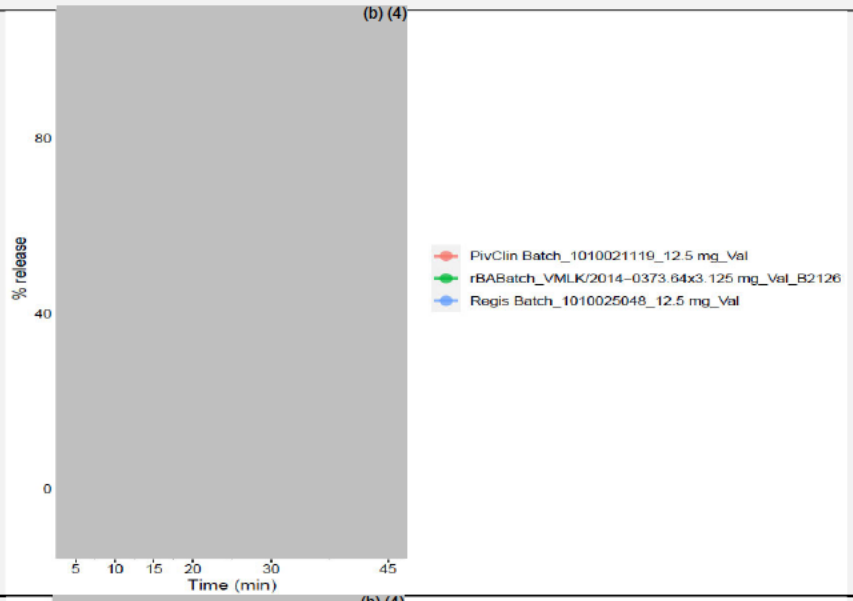
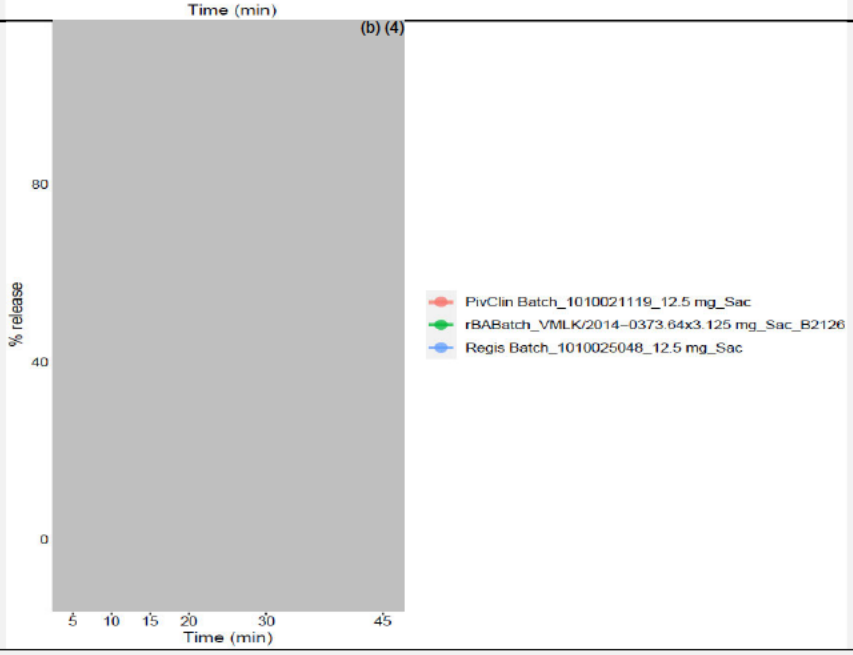
DISSOLUTION ACCEPTANCE CRITERION:

The Applicant proposed '*Q*= (b) (4) *% in 20 minutes*' as the dissolution acceptance criterion for each strength of the proposed granule product. Dissolution data for valsartan and sacubitril for batches that demonstrate discriminating ability of the proposed dissolution method with respect to the effect of (b) (4) can reject the proposed acceptance criterion '*Q*= (b) (4) *% in 20 minutes*', though the variations evaluated are greater than 100% and not meaningful.

Moreover, dissolution of valsartan and sacubitril from the clinical batches dosed in the rBA studies, B2126 and F2130, with no (b) (4) % talc (b) (4) would be rejected by the proposed acceptance criterion "Q= (b) (4) % in 20 minutes" as compared to the clinical batches (> (b) (4) % in 10 minutes) dosed in the pivotal safety, efficacy, and pharmacokinetic study B2319 that contain (b) (4) and the TBM commercial batches, that contain (b) (4) % talc (b) (4) (see **Figure 4j**).

Hence, the proposed acceptance criterion '*Q*= (b) (4) *% in 20 minutes*' is adequate for dissolution testing of the drug product.

Figure 4j. Comparative dissolution profile for valsartan and sacubitril from 12.5 mg clinical and registration batches to support the proposed acceptance criterion '*Q= (b) (4) % in 20 minutes*'
[USP App 1 (basket) at 50 rpm in 900 mL buffer solution, pH 6.8 at 37°C]

API	Dissolution Profile,12.5 mg Clinical and Registration Batches
Valsartan	
Sacubitril	

B.3 CLINICAL RELEVANCE OF DISSOLUTION METHOD & ACCEPTANCE CRITERION *(e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)*

Based on the overall dissolution data and pharmacokinetic data provided for clinical and registration batches from the rBA studies, B2126, F2130, and B2319, the proposed

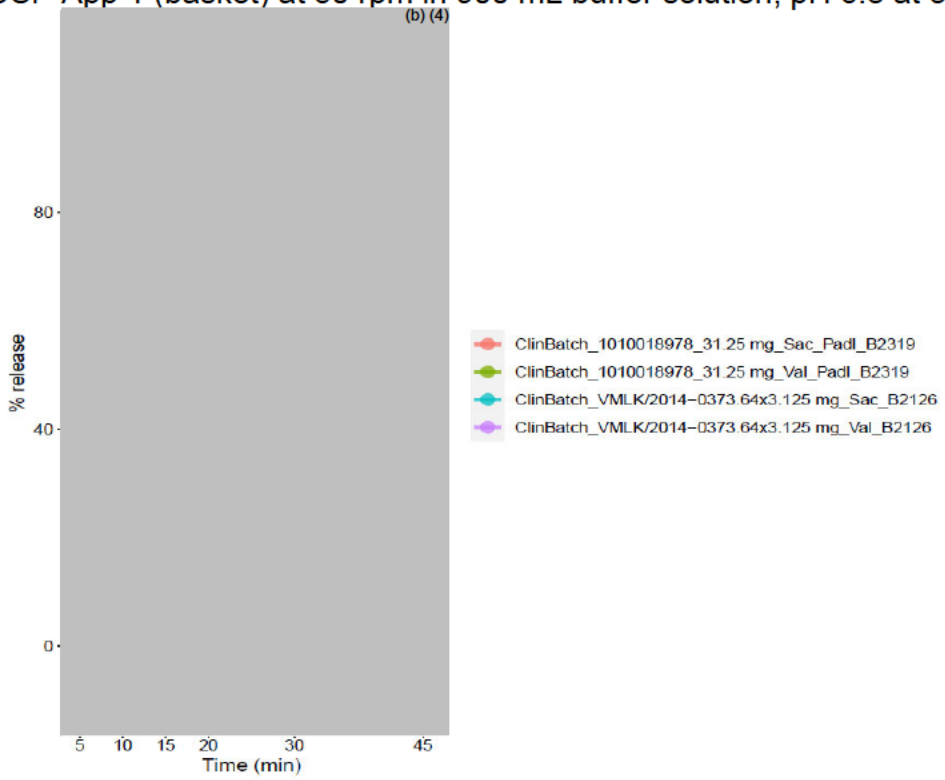
dissolution method can be considered bio-relevant; however, the bio-predictiveness of the method cannot be confirmed as there is insufficient data.

Though clinical batches of the pediatric formulation containing no (b) (4)% talc and administered in the rBA studies, B2126 and F2130, would be rejected by the proposed dissolution acceptance criterion '*Q=(b) (4)% in 20 minutes*', the clinical batch administered in the rBA study, B2126 would meet the 80-125% BE criteria for Cmax and $AUC_{0\text{-}inf}$ and was deemed bioequivalent to the adult formulation (see Clinical Pharmacology Review for NDA 207620-S013). However, the rBA studies, B2126 and F2130 were conducted in adult volunteers, and not in pediatric patients.

A pivotal safety, efficacy, and rBA study, B2319, was conducted in pediatric patients to support the Label Claim and provide a bridge to the formulations administered in rBA study B2126.

Clinical batches dosed in the pivotal rBA study, B2319, containing (b) (4) and the TBM commercial batches, that contain (b) (4)% talc (b) (4) would meet the proposed dissolution acceptance criterion '*Q=(b) (4)% in 20 minutes*' (see **Figure 5**). Clinical batches administered in the pivotal rBA study, B2319 would meet the 80-125% BE criteria for $AUC_{0\text{-}inf}$. The TBM commercial batches are currently administered in the pivotal safety and efficacy study, B2319E1.

Figure 5. Comparative dissolution profile for valsartan and sacubitril from 12.5 mg and 31.25 mg clinical batches to support bio-predictiveness of the dissolution method [USP App 1 (basket) at 50 rpm in 900 mL buffer solution, pH 6.8 at 37°C]



Therefore, there is insufficient data to conclude that the proposed method is bio-predictive. However, a 'safe-space' can be constructed around the type of (b) (4) with the overall dissolution data and pharmacokinetic data provided in the submission.

B.4 APPLICATION OF DISSOLUTION/IVIVC IN QbD

(b) (4) was identified as a critical formulation variable that could have an impact on the dissolution of the drug product and therefore the (b) (4) was optimized. A variant batch 15503.001 was (b) (4) and dissolution was conducted in phosphate buffer, pH 6.8 for 3 minutes. Faster dissolution in 3 minutes was observed (b) (4). Based on the dissolution data, (b) (4)

(b) (4)

A batch was manufactured and (b) (4); however, the batch did not meet the dissolution specifications. A root-cause analysis identified (b) (4) as cause for out-of-specification for dissolution. (b) (4) This variant batch demonstrated dissolution that meet the specifications (b) (4)

BB.12 BRIDGING OF FORMULATIONS

Assessment: *{Adequate}*

Bridging of pediatric and adult formulation, and formulations due to (b) (4)

The proposed 2 mm Entresto™ (sacubitril and valsartan, LCZ696 (b) (4) granules, 12.5 mg (6.1 mg/6.4 mg; sacubitril/valsartan) and 31.25 mg (15.18 mg/16.07 mg; sacubitril/valsartan) drug product is intended for pediatric administration. The 12.5 mg strength drug product in a hypromellose capsule is made up of 4×3.125 mg granules, whereas the 31.25 mg drug product includes 10×3.125 mg granules.

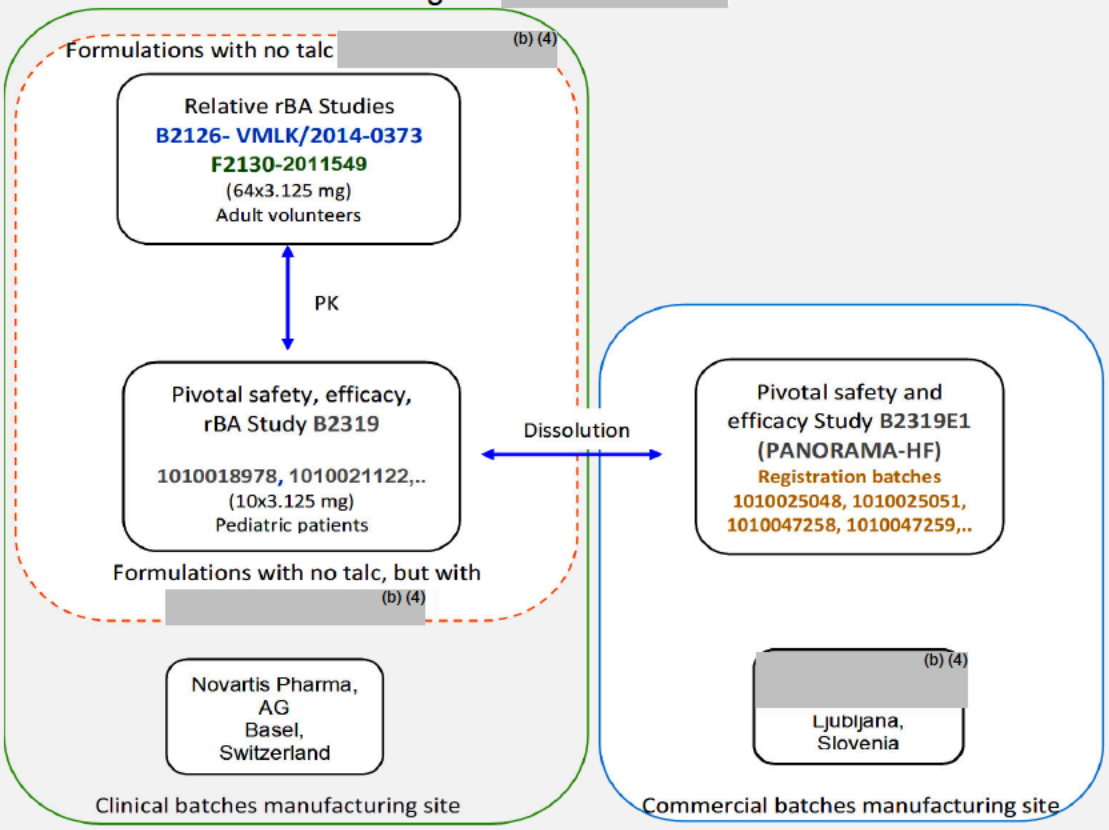
The adult formulation of Entresto™ (sacubitril and valsartan, LCZ696 (b) (4) tablets, 24/26 mg; 49/51 mg; 97/103 mg was previously approved under NDA 207620 (dated 07/07/2015).

(b) (4)

The to-be-marketed (TBM) of the granule formulation includes talc (b) (4) (b) (4) However, formulations used in the two relative bioavailability studies, B2126 and F2130 and in the pivotal safety, efficacy, and pharmacokinetic study B2319 do not contain talc. The TBM drug product that contain talc have been dosed in the pivotal safety and efficacy study, B2319E1.

The bridging of the pediatric formulations to the adult formulation was supported by a number of relative bioavailability studies, B2126 and F2130 in adult population. Bridging of the different pediatric formulations in pediatric patients is also supported by the pivotal bioavailability study B2319. The final commercial product contains talc (b) (4) in Hypromellose capsules. Bridging of the final commercial product with talc is supported by comparative dissolution data of the registration batches and clinical batches that were administered in pivotal clinical study B2319 (see **Figure 6**).

Figure 6. Bridging of pediatric and adult formulations and formulations due to change in (b) (4)



Relative Bioavailability Studies, B2126 and F2130:

Two relative bioavailability (rBA) studies, B2126 and F2130 were conducted with the proposed 3.125 mg (1.518 mg/1.607 mg; sacubitril/valsartan) granules product to provide a bridge to the adult formulation (see **Table 7a**).

Table 7a. Batch details, dissolution data, and pharmacokinetic parameters for the formulations administered in the two relative bioavailability (rBA) studies, B2126 and F2130

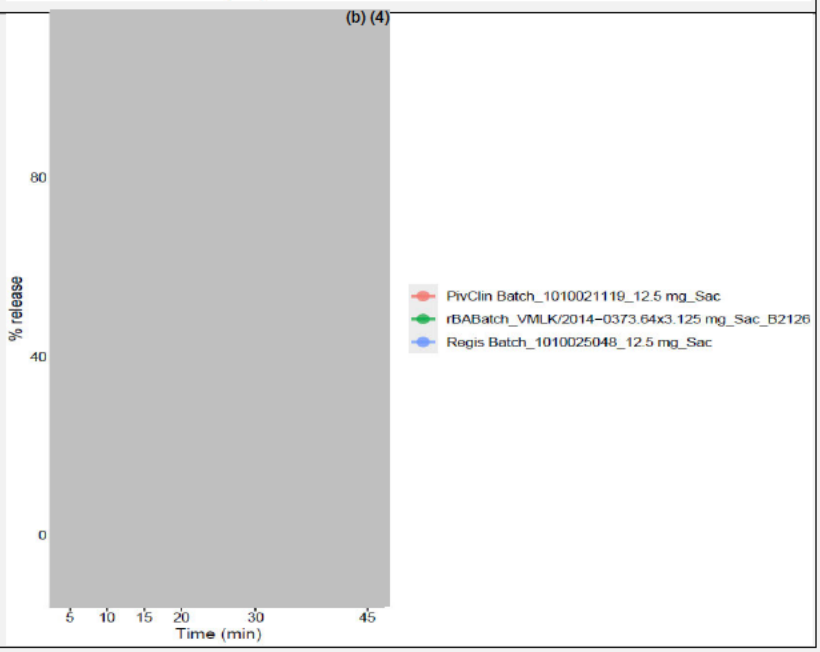
Batch number for 3.125 mg (1.518 mg/1.607 mg; sacubitril/valsartan) granules	Relative BA study numbers	Dissolution data at 20 minutes with previous (paddle) dissolution method		Pharmacokinetic parameters for sacubitril/valsartan in rBA Studies		
		Percent (%) valsartan released	Percent (%) sacubitril released	Valsartan	Sacubitril	Sacubitrilat LBQ657
VMLK/2014-0373; 64×3.125 mg (1.518 mg/ 1.607 mg)	CLCZ69 6B2126 or B2126 N=40	(b) (4)	(b) (4)	Cmax (ng/mL) 1.09 (0.98-1.21)	Cmax (ng/mL) 0.94 (0.80-1.11)	Cmax (ng/mL) 0.95 (0.91-0.99)

granules, 200 mg (no talc) Batch Number H875CH, 200 mg adult formulation (97.2 mg/102.8 mg; sacubitril/valsartan) tablets	Under fasted condition			$AUC_{0\text{-}inf}$ (ng*hr/mL) 1.11 (1.00-1.24)	$AUC_{0\text{-}inf}$ (ng*hr/mL) 0.96 (0.92-1.00)	$AUC_{0\text{-}inf}$ (ng*hr/mL) 0.98 (0.96-0.99)
2011549; 64× 3.125 mg (1.518 mg/ 1.607 mg) granules (200 mg) dissolved in 100 mL water (no talc) dispensed as a suspension Batch Number H257LK, 200 mg adult formulation (97.2 mg/102.8 mg; sacubitril/valsartan) tablets	CLCZ696F2130 or F2130 N=28 Healthy male and female subjects between 18 and 45 years	(b) (4)	(b) (4)	Cmax (ng/mL) 1.00 (0.91-1.10) $AUC_{0\text{-}inf}$ (ng*hr/mL) 0.91 (0.83-1.00)	Cmax (ng/mL) 1.72 (1.48-1.98) $AUC_{0\text{-}inf}$ (ng*hr/mL) 1.04 (1.00-1.07)	Cmax (ng/mL) 1.13 (1.08-1.18) $AUC_{0\text{-}inf}$ (ng*hr/mL) 1.00 (0.99-1.02)

The Applicant noted the granules drug product batches (see **Table 6a**) administered in the two relative bioavailability (rBA) studies, B2126 and F2130 are (b) (4) similar to the to-be-marketed (TBM) drug product, except for the absence of talc.

Dissolution of valsartan and sacubitril from the two formulations administered in the rBA studies, B2126 and F2130, is slower (> (b) (4) % in 45 minutes) than the granule product ((b) (4) % in 15 minutes) administered in the pivotal clinical study B2319 and commercial batches using the proposed dissolution method (see **Figure 7**).

Figure 7. Comparative dissolution profile for valsartan and sacubitril from 12.5 mg clinical batches to support formulation bridging
[USP App 1 (basket) at 50 rpm in 900 mL buffer solution, pH 6.8 at 37°C]

API	Dissolution Profile,12.5 mg Clinical and Registration Batches
Valsartan	
Sacubitril	

The formulation in rBA study, B2126 will meet the BE criteria of 90% confidence interval between 80% and 125% for peak concentration (Cmax) and exposure ($AUC_{0\text{-}inf}$) for valsartan, sacubitril, and active metabolite LBQ657 from the pediatric granules when compared to the adult formulation. However, the Cmax for sacubitril for the liquid formulation (3.125 mg×64 granules, 200 mg, dissolved in 100 mL water) administered in the rBA study, F2130 is 72% higher and will not meet the BE criteria (90% confidence interval between 80% and 125%); though

PK parameters for valsartan and the active metabolite LBQ657 for the pediatric granules are equivalent to that of the adult formulation. (b) (4)

Pivotal Bioavailability Study, B2319:

The 12.5 mg (6.1 mg/6.4 mg; sacubitril/valsartan) and 31.25 mg (15.18 mg/16.07 mg; sacubitril/valsartan) film-coated granule product was also administered in the pivotal safety, efficacy, and pharmacokinetic study CLCZ696B2319 or B2319 (PANORAMA-HF). The drug product that was administered in the pivotal clinical study B2319 is composed of (b) (4) (and not talc) (b) (4) (see **Table 7b**).

Dissolution of valsartan and sacubitril from the 12.5 mg strength granule batches such as 1010017611, 1010021119, and 31.25 mg batches including 1010021122 administered in the pivotal rBA study B2319 is rapid (> (b) (4) % in 15 minutes) using the proposed dissolution method.

Table 7b. Batch details, dissolution data, and pharmacokinetic parameters for the formulations administered in the pivotal bioavailability (BA) study, B2319

Batch numbers proposed 3.125 mg (1.518 mg/1.607 mg; sacubitril/valsartan) granules	Pivotal study number	Dissolution data at 20 minutes with proposed (basket) dissolution method		Pharmacokinetic Parameters for Sacubitril/Valsartan in rBA Studies		
		Percent (%) Valsartan Released	Percent (%) Sacubitril Released	Valsartan	Sacubitril	Sacubitrilat LBQ657
12.5 mg 1010017611, 1010021119, others; 31.25 mg 1010021122, others 3.125 mg granules (no talc, but (b) (4)) @ (b) (4) mg/kg and (b) (4) mg/kg Batch Number Several 200 mg adult formulation (97.2 mg/102.8	CLCZ696 B2319 or B2319 N=392 Pediatric patients 1 month to<18 years with heart failure	(b) (4) %	(b) (4) %	Refer to Clinical Pharmacology Review for information on PK parameters for valsartan, sacubitril, and sacubitrilat		

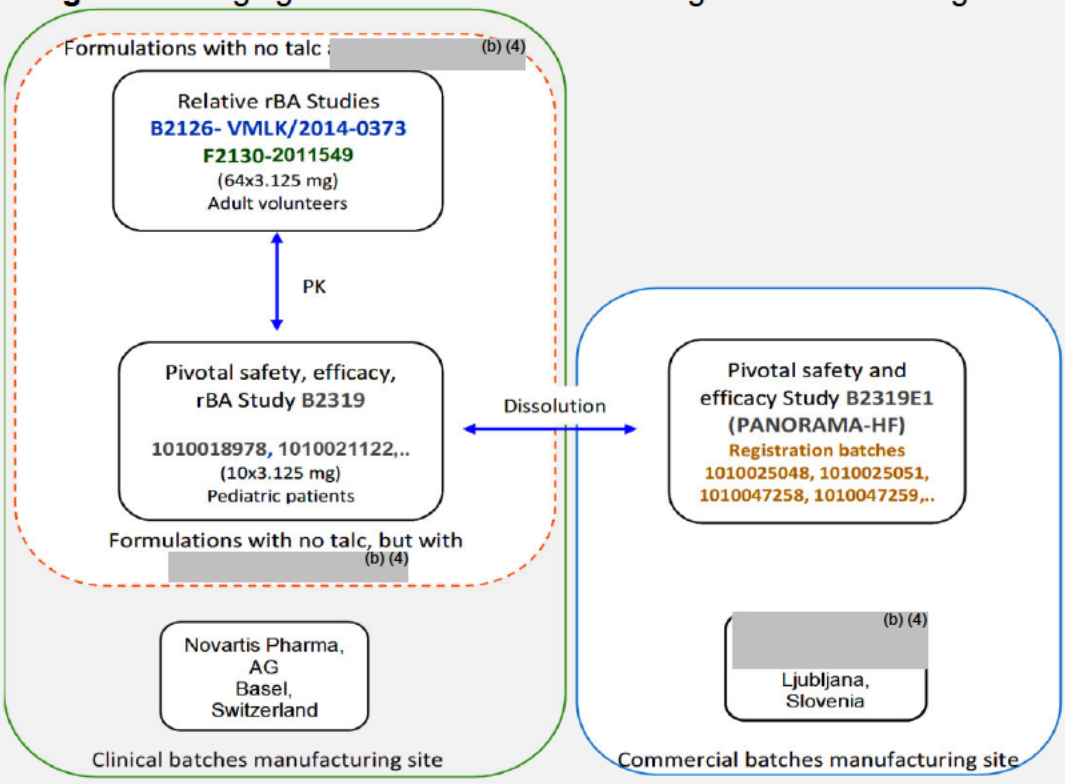
mg; sacubitril/valsartan), bid				

Bridging of formulations due to a change in the manufacturing site:

The commercial, TBM drug product will be manufactured at (b) (4) Ljubljana, Slovenia. The manufacturing site was also involved in the manufacture of pilot scale batches, registration stability batches, and clinical batches that are currently administered in the pivotal safety and efficacy study B2319E1. The TBM drug product contains (b) (4) talc (b) (4)

However, the clinical batches administered in the rBA and pivotal BA studies B2126, F2130, and B2319, respectively, were manufactured at Novartis Pharma, AG, Basel, Switzerland (see **Figure 8**). Moreover, the clinical batches dosed in the pivotal BA study B2319 contain (b) (4); whereas, the clinical batches administered in the rBA studies B2126 and F2130, do not contain (b) (4) talc (b) (4).

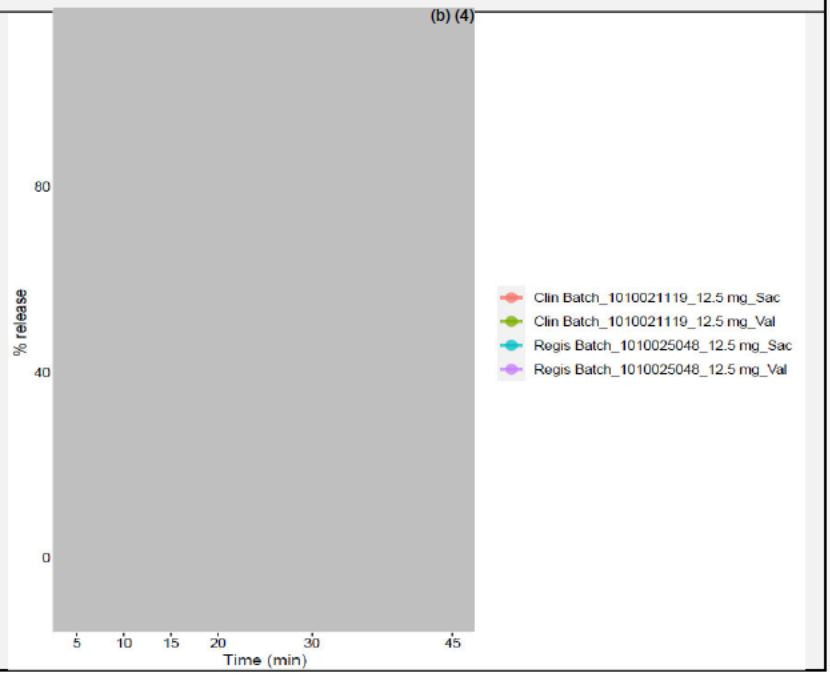
Figure 8. Bridging of formulations due to change in manufacturing site

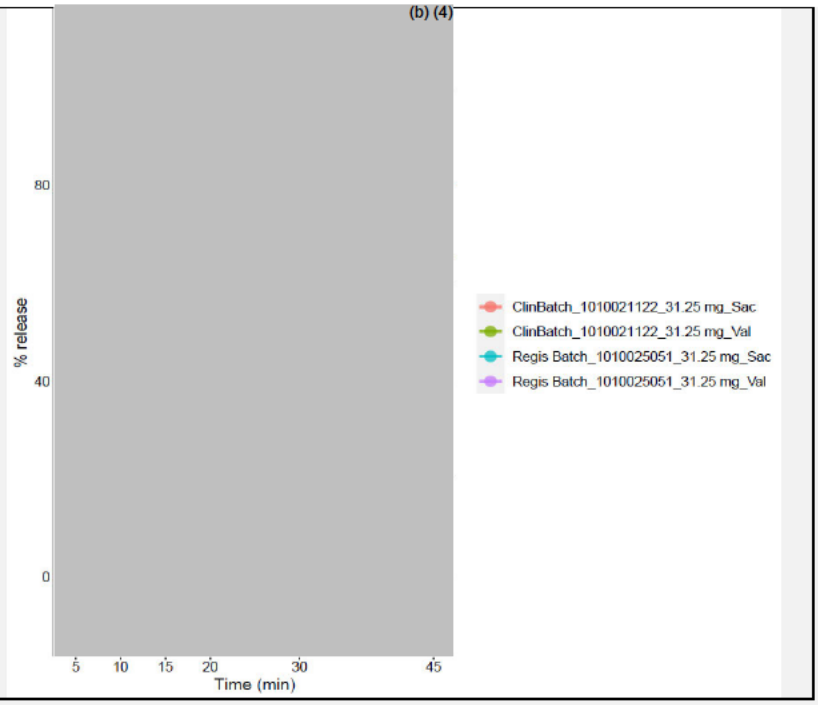


Dissolution of valsartan and sacubitril from the 12.5 mg and 31.25 mg commercial, TBM drug product batches 1010025048 and 1010025051, respectively, containing (b) (4) talc (b) (4) is very rapid (> (b) (4)% in 15 minutes) and similar (*f2*>50) to the 12.5 mg and 31.25 mg clinical batches 1010021119 and

1010021122, respectively, containing (b) (4) (see **Figure 9**). As some of the registration batches are currently administered in the pivotal safety and efficacy study B2319E1, the commercial manufacturing site for the TBM drug product containing (b) (4) talc (b) (4) is 'bridged' through dissolution data, and safety and efficacy study, B2319E1 to the manufacturing site for the clinical batches containing (b) (4)

Figure 9. Comparative dissolution profile for valsartan and sacubitril from 12.5 mg and 31.25 mg clinical batches to support manufacturing site change [USP App 1 (basket) at 50 rpm in 900 mL buffer solution, pH 6.8 at 37°C]

	Dissolution profile for valsartan and sacubitril from 12.5 mg and 31.25 mg clinical and registration batches
12.5 mg clinical and registration batches	

31.25 mg clinical and registration batches	

B. 13 BIOWAIVER REQUEST

Assessment: *{Not Applicable}*

There are no biowaiver requests in the current submission.

R. REGIONAL INFORMATION

Comparability Protocols

Assessment: *{Not Applicable}*

Post-Approval Commitments

Assessment: *{Not Applicable}*

Lifecycle Management Considerations

Assessment: *{Not Applicable}*

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Parnali Chatterjee

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Haritha Mandula

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Theodore Carver

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