CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207620Orig1s000

CHEMISTRY REVIEW(S)

Product Quality Recommendation: APPROVAL

NDA 207620
Review # 01 Addendum
Review Date: June 30, 2015

Drug Name/Dosage Form	Entresto (sacubitril and valsartan) Tablets
Strength	24 mg sacubitril and 26 mg valsartan 49 mg sacubitril and 51 mg valsartan 97 mg sacubitril and 103 mg valsartan
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Novartis Pharmaceuticals Corporation
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Amendment	25-JUN-2015
Amendment	26-JUN-2015
Amendment	15-JUN-2015
Amendment	11-JUN-2015
Amendment	04-JUN-2015
Amendment	02-JUN-2015
Amendment	26-MAY-2015
Amendment	15-MAY-2015
Amendment	15-MAY-2015

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Anamitro Banerjee	ONDP Branch III/Division I
Drug Product	Sherita McLamore-Hines	ONDP Branch I/Division I
Process	Bogdan Kurtyka	OPF Branch 1/Division of Process Assessment I
Microbiology	Robert Mello	OPF Branch /Division of Microbiology Assessment
Facility	Zhong Li	OPF Branch /Division of Inspectional Assessment
Biopharmaceutics	Salaheldin Hamed	ONDP Branch III/Division of Biopharmaceutics
Project/Business Process Manager	Maryam Kord Bacheh Changi	OPRO Branch I/Division I
Application Technical Lead	Wendy Wilson-Lee	ONDP Branch I /Division I
Laboratory (OTR)	-	-
ORA Lead	Karen D'Orzio	ORA
Environmental Assessment (EA)	Raanan Bloom	ONDP EA Team

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Quality Review Data Sheet

1. **LEGAL BASIS FOR SUBMISSION:** 505(b)(1)

2. **RELATED/SUPPORTING DOCUMENTS:**

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS[1]	REVIEW DATE	COMMENTS
23902	Type II	Novartis Pharmaceutical Corporation	Valsartan	1	25-NOV-2014	

[1] Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	104628	LCZ696 (sacubitril/valsartan) for heart failure and chronic heart failure
IND		(b) (4)

3. **CONSULTS:**

No consults requested.

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

We recommend **approval of NDA 207620 from a product quality perspective** for Entresto™ (sacubitril/valsartan) Tablets, 97/103, 49/51, and 24/26 mg when stored in the intended packaging and stored at USP Controlled Room Temperature.

Additional OPQ Language for Action Letter

The comparability protocols supporting post-approval changes to 1) the drug product manufacturing site, control, batch size, and process and 2) the (b) (4) intermediate manufacturing site, control, batch size, and process are acceptable.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Post-Marketing Commitment Subject to 506B: None

Post-Marketing Agreements Not Subject to 506B: Development of a new dissolution method for all strengths with demonstrated discriminating ability, (b) (4) Using the new dissolution method and data from the overall multipoint dissolution profile from a minimum of 12 commercial batches per strength, manufactured under the same conditions as those used for the manufacture of the batches used in pivotal clinical trials, set the final dissolution acceptance criterion for Entresto™ (sacubitril/valsartan) Tablets, 97/103, 49/51, and 24/26 mg.

II. Summary of Quality Assessments

A. Drug Substance [Sacubitril (b) (4) and Valsartan] Quality Summary

1. Chemical Name or IUPAC Name/Structure

Sacubitril: 4-{[(1*S*,3*R*)-1-([1,1'-Biphenyl]-4-ylmethyl)-4-ethoxy-3-methyl-4-oxobutyl]amino}-4-oxobutanoic acid
Valsartan: *N*-Pentanoyl-*N*-{[2'-(1*H*tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl}-L-valine

2. Properties/CQAs Relevant to Drug Product Quality

The CQAs relevant to drug product quality are physical form, bulk density, and (b) (4) (b) (4).

3. List of starting materials

(b) (4)

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