

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206302Orig1s000

CHEMISTRY REVIEW(S)

Recommendation: APPROVAL

NDA 206302 Resubmission Review #2

Drug Name/Dosage Form	Byvalson™ (Nebivolol/Valsartan) Tablets
Strength	5 mg/80 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Forest Laboratories LLC
US agent, if applicable	None.

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Amendment	11-Mar-2016	Drug Product
Amendment	29-JAN-2016	Drug Product
Amendment	26-OCT-2015	Drug Product
Resubmission	29-SEP-2015	Drug Product, Facilities

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance Drug Product Environmental Assessment Labeling	Rao Kambhampati	ONDP/DNDP1/Branch1
Facility	Thuy Nguyen	OPF/DIA/B1
Regulatory Business Process Manager	Maryam Kord Bacheh Changi	OPRO/DRBPM1/Branch1
Application Technical Lead	Wendy Wilson-Lee	ONDP/DNDP1/Branch1

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Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	REVIEW DATE	COMMENTS
(b) (4)	Type II	[REDACTED]	(b) (4)	Adequate	08-OCT-2014	
	Type II			Adequate	23-OCT-2014	

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	20665	Diovan (valsartan) Capsules
NDA	21283	Diovan (valsartan) Tablets
NDA	21742	Bystolic (nebivolol) Tablets
IND	109771	Nebivolol/valsartan fixed dose combination
IND	33060	Nebivolol

2. CONSULTS: None.

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

OPQ recommends **APPROVAL** of NDA 206302 for Byvalson (nebivolol/valsartan) Tablets, 5 mg/80 mg.

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

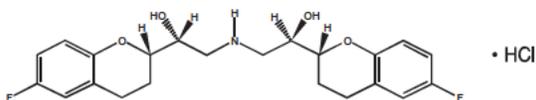
OPQ does not have any Phase 4 commitments, agreements, or risk-management steps.

II. Summary of Quality Assessments

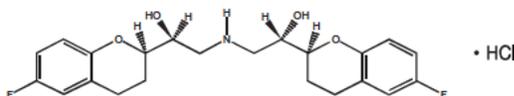
A. Drug Substance [Nebivolol Hydrochloride and Valsartan] Quality Summary

Nebivolol

The drug product contains nebivolol hydrochloride as one of the two active ingredients. Nebivolol hydrochloride, known chemically as (1*RS*,1'*RS*)-1,1'-[(2*RS*,2'*SR*)-bis(6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-yl)]-2,2'-iminodiethanol hydrochloride. Nebivolol hydrochloride is present as a racemic mixture of *d*-Nebivolol hydrochloride and *l*-Nebivolol hydrochloride with the stereochemical designations of [SRRR]-nebivolol hydrochloride and [RSSS]-nebivolol hydrochloride, respectively. Both stereoisomers have a molecular formula of C₂₂H₂₅F₂NO₄•HCl and a molecular weight of 441.90. Nebivolol hydrochloride is a white to almost white powder that is soluble in methanol, sparingly soluble in ethanol, and very slightly soluble in dichloromethane.



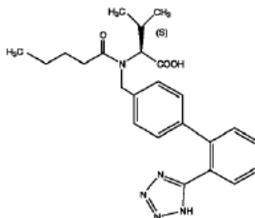
(SRRR) - or *d*-nebivolol hydrochloride



(RSSS) - or *l*-nebivolol hydrochloride

Valsartan

The drug product also contains valsartan as an active ingredient. Valsartan, known chemically as *N*-(1-Oxopentyl)-*N*-[[2'-(1*H*-tetrazol-5-yl) [1,1'-biphenyl]-4-yl]methyl]-*L*-valine, has a molecular formula of C₂₄H₂₉N₅O₃ and a molecular weight of 435.52. Valsartan is a white or almost white fine powder that is freely soluble in ethanol, sparingly soluble in methylene chloride, and practically insoluble in water.





ASSESSMENT OF ENVIRONMENTAL ANALYSIS

1. Is the applicant's claim for categorical exclusion acceptable?
2. Is the applicant's Environmental Assessment adequate for approval of the application?

Applicant's Response: EICs for all active ingredients in all drug product strengths:

Table 1.12.14-1. Calculation of Expected Introduction Concentration (EIC) for Nebivolol

EIC - Aquatic (ppb) = A × B × C × D				
where	A = kg/year produced for direct use (as active moiety) B = 1/litres per day entering POTWS C = year/365 days D = 10 ⁹ µg/kg (conversion factor)			
B = 1.214 × 10 ¹¹ litres per day entering publicly owned treatment works (POTWs). (Source: 1996 Needs Survey, Report to Congress)				
EIC	(b) (4)			
Drug Product	# of tablets/year^a	API (mg/tablet)^b	API (kg/year)	EIC (ppb)
Nebivolol/Valsartan Tablets, 5/80 mg				(b) (4)
Nebivolol/Valsartan Tablets, 5/160 mg				
Nebivolol/Valsartan Tablets, 10/160 mg				
Nebivolol/Valsartan Tablets, 10/320 mg				
Nebivolol/Valsartan Tablets, 20/320 mg				
Total API Quantity				(b) (4)
^a	(b) (4)			
^b	Calculated as nebivolol HCl			

Table 1.12.14-2. Calculation of Expected Introduction Concentration (EIC) for Valsartan

EIC - Aquatic (ppb) = A × B × C × D				
where	A = kg/year produced for direct use (as active moiety) B = 1/litres per day entering POTWS C = year/365 days D = 10 ⁹ µg/kg (conversion factor)			
B = 1.214 × 10 ¹¹ litres per day entering publicly owned treatment works (POTWs). (Source: 1996 Needs Survey, Report to Congress)				
EIC	(b) (4)			
Drug Product	# of tablets/year^a	API (mg/tablet)^b	API (kg/year)	EIC (ppb)
Nebivolol/Valsartan Tablets, 5/80 mg				(b) (4)
Nebivolol/Valsartan Tablets, 5/160 mg				
Nebivolol/Valsartan Tablets, 10/160 mg				
Nebivolol/Valsartan Tablets, 10/320 mg				
Nebivolol/Valsartan Tablets, 20/320 mg				
Total API Quantity				(b) (4)
^a	(b) (4)			

Reviewer’s Assessment: Acceptable. The applicant requested a categorical exclusion based on (21 CFR 25.15 (b) and (d)) for all drug product strengths in the original NDA submission. This was found to be acceptable. In the resubmission and in the 3/11/16 amendment, the applicant did not propose any changes. The EICs for the 5/80 mg strength tablet were (b) (4) and (b) (4) ppb, respectively. Therefore, the claimed categorical exclusion from EA requirement is acceptable.

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer’s Assessment and Signature: The total EIC for nebivolol is (b) (4) and for valsartan is (b) (4), which are lower than the permitted EIC of 1 ppb for each ingredient. No extraordinary circumstances exist. The EA is recommended for approval.

Rao V. Kambhampati, Ph.D.
Senior Chemist/ONDP/DNDP I/NDPB I

Secondary Review Comments and Concurrence: I concur.

Wendy I. Wilson-Lee, Ph.D.
Branch Chief (Acting), ONDP/DNDP1/Branch1

ASSESSMENT OF LABELING

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert

1. Package Insert

(a) “Highlights” Section (21CFR 201.57(a))

Item	Information Provided in NDA	Reviewer’s Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Byvalson™ (nebivolol and valsartan)	Acceptable
Dosage form, route of administration	Tablets, oral	Acceptable
Controlled drug substance symbol (if applicable)	N/A	N/A
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Each tablet contains 5.45 mg of nebivolol hydrochloride, which is equivalent to 5 mg of nebivolol free base and 80 mg of valsartan.	Acceptable.

Conclusion: Acceptable. The above information will be reflected in the final package insert.

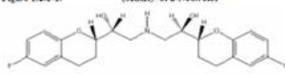
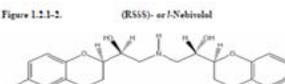
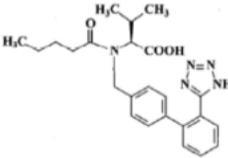
(b) “Full Prescribing Information” Section

3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

Item	Information Provided in NDA	Reviewer’s Assessment
Available dosage forms	Immediate release oral tablet	Acceptable.
Strengths: in metric system	5 mg/80 mg	Acceptable.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Capsule shaped, purple coated tablet, debossed with “FL1” on one side.	Acceptable.

Conclusion: Acceptable. The above information will be reflected in the final package insert.

#11: Description (21CFR 201.57(c)(12))

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Byvalson™ (neбиволол and valsartan)	Acceptable.
Dosage form and route of administration	Tablets/oral administration	Acceptable.
Active moiety expression of strength with equivalence statement for salt (if applicable)	Each tablet contains 5.45 mg of neбиволол hydrochloride, which is equivalent to 5 mg of neбиволол free base and 80 mg of valsartan.	Acceptable.
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	The inactive ingredients include: Lactose monohydrate, microcrystalline cellulose, copovidone, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, talc, ferric oxide, hypromellose, polysorbate 80, and Opadry® II Purple film-coat. The Opadry® II is made of polyvinyl alcohol-part hydrolyzed, titanium dioxide, macrogol/PEG, talc, ferrousferic oxide/black iron oxide, and iron oxide red.	Acceptable.
Statement of being sterile (if applicable)	N/A	N/A
Pharmacological/ therapeutic class	Byvalson is a beta adrenergic blocker and an angiotensin II receptor blocker.	Acceptable.
Chemical name, structural formula, molecular weight	<p>1) Neбиволол Hydrochloride: (1<i>RS</i>,1'<i>RS</i>)-1,1'-[(2<i>RS</i>,2'<i>SR</i>)-bis(6-fluoro-3,4-dihydro-2<i>H</i>-1-benzopyran-2-yl)]-2,2'-iminodiethanol hydrochloride, present as a racemic mixture of <i>d</i>-neбиволол hydrochloride and <i>l</i>-neбиволол hydrochloride with the stereochemical designations of [SRRR]-neбиволол hydrochloride and [RSSS]-neбиволол hydrochloride, respectively</p> <p>Figure 1.2.1-1. (SRRR)- or <i>d</i>-Neбиволол</p>  <p>Figure 1.2.1-2. (RSSS)- or <i>l</i>-Neбиволол</p>  <p>C₂₂H₂₅F₂NO₄ • HCl Mol. Wt. = 441.90 (for hydrochloride)</p> <p>2) Valsartan: <i>N</i>-(1-Oxopentyl)-<i>N</i>-[[2'-(1<i>H</i>-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-L-valine.</p>  <p>C₂₄H₂₉N₅O₃ Mol. Wt. = 435.52</p>	Acceptable.
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa, solubility, or pH)	1) Neбиволол hydrochloride: Soluble in methanol, dimethylsulfoxide, N,N-dimethylformamide; sparingly soluble in ethanol, propylene glycol, polyethylene glycol; very slightly soluble in hexane, dichloromethane, and methylbenzene.	Acceptable.

	2) Valsartan: Solubility: Freely soluble in anhydrous ethanol, sparingly soluble in methylene chloride, and practically insoluble in water.	
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Conclusion: Acceptable. The final revised package insert will reflect all the above information.

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	5 mg nebigolol/80 mg valsartan per tablet	Acceptable
Available units (e.g., bottles of 100 tablets)	Bottles of 30 Bottles of 90	Acceptable
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Purple/capsules shaped tablet, marked FL1 on one side.	Acceptable
Special handling (e.g., protect from light, do not freeze)	Dispense in a tightly closed container	Acceptable
Storage conditions	Store at 20° to 25°C (68° to 77°F) [see USP for Controlled Room Temperature]	Acceptable

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Distributed by: Actavis Pharma, Inc. Parsippany, NJ 07054 USA	Acceptable.

Conclusion: Acceptable. The above information will be reflected in the final revised package insert.

2. Container and Carton Labeling

1) Immediate Container Label

In the 3/11/16 amendment to the resubmission, the following immediate container labels were submitted for the 5 mg/80 mg strength tablet bottles: 30ct Trade Bottle Label, 90ct Trade Bottle Label, and 7ct Sample Bottle Label.

30-Count Trade Bottle Label:



90-Count Trade Bottle Label:



7-Count Sample Bottle Label:



[Redacted] (b) (4)

Reviewer's Assessment: From quality review stand point, the above label contains all the required information. [Redacted] (b) (4)

Item	Comments on the Information Provided in NDA	Conclusion
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Byvalson™ (nebivolol and valsartan)	Acceptable.
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	5 mg/80 mg	Acceptable.
Route of administration 21.CFR 201.100(b)(3))	Oral	Acceptable.
Net contents* (21 CFR 201.51(a))	7ct per sample bottle and 30ct and 90ct per trade bottle.	Acceptable.
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	Oral tablet, therefore, not provided	Acceptable.
Lot number per 21 CFR 201.18	Yes	Acceptable.
Expiration date per 21 CFR 201.17	Yes	Acceptable.
*"Rx only" statement per 21 CFR 201.100(b)(1)	Rx only	Acceptable.
Storage (not required)	Store at 20° to 25°C (68° to 77°F) [see USP for Controlled Room Temperature]	Acceptable.

In addition to the above, the applicant provided electronic sample labels of the following secondary packages:

- 7ct Sample Tray: This is for a professional sample. Each tray contains 12 boxes, which contain 7 tablets each
- 5ct (b) (4) Tray: This is for a professional sample. Each tray contains 5 boxes, which contain 30 tablets each
- 5ct (b) (4) Sleeve: This is for a professional sample. Each sleeve contains 5 boxes, which contain 30 tablets each

Reviewer's Assessment: Cartons will be used for secondary packaging of professional sample bottles only. From the quality review stand point, the above labels contain all the required information.

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	Byvalson™ (nebivolol and valsartan)	Acceptable.
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(d)(2))	5 mg/80 mg	Acceptable.
Net contents (21 CFR 201.51(a))	7ct and 30ct per professional sample bottle	Acceptable.
Lot number per 21 CFR 201.18	Yes	Acceptable.
Expiration date per 21 CFR 201.17	Yes	Acceptable.
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]	Not applicable because dosage form is oral tablet.	Acceptable.
Sterility Information (if applicable)	Not applicable. Oral tablet.	Acceptable.
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)	Rx only	Acceptable.
Storage Conditions	Store at 20° to 25°C (68° to 77°F) [see USP for Controlled Room Temperature]	Acceptable.
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Yes	Acceptable.
Bar Code per 21 CFR 201.25(c)(2)**	Yes	Acceptable.
Name of manufacturer/distributor	Distributed by (b) (4)	Acceptable.
"See package insert for dosage information" (21 CFR 201.55)	Included.	Acceptable.
"Keep out of reach of children" (optional for Rx, required for OTC)	Included.	Acceptable.
Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))	Not included because oral tablet.	Acceptable.

Conclusion: Acceptable. The final revised labels will contain all the suggested changes.

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer’s Assessment and Signature: The proposed package insert and the primary and secondary container labels proposed in the 3/11/16 amendment to the resubmission are similar to those submitted in the recent amendment for the (b) (4) tablets. The final revised package insert and the final primary and secondary container labels will reflect all the proposed changes. From the quality review stand point, the revised package insert and the revised container labels are recommended for approval.

Rao V. Kambhampati, Ph.D.
Senior Chemist/INDP/DNDP I/NDPB I

Secondary Review Comments and Concurrence: I concur.

Wendy I. Wilson-Lee, Ph.D.
Branch Chief (Acting), ONDP/DNDP1/Branch1

II. List of Deficiencies To Be Communicated

None.

III. Attachments

A. Lifecycle Knowledge Management

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Assay	(b) (4)	Release – Low Shelf-Life – Low	HDPE bottles (b) (4)	Acceptable	Changes to container closure should be evaluated
Physical Stability (solid state)		Nebivolol – Medium Valsartan – Medium			None
Content Uniformity		Nebivolol – medium Valsartan - Low	(b) (4)	Acceptable	(b) (4)
Microbial Limits		Low		Acceptable	None

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Dissolution	Inherent solubility of drug substance, Particle size, (b) (4) tablet hardness, disintegration	Medium		Acceptable	(b) (4)
(b) (4)	(b) (4)	Low		Acceptable	

NDA 206302

ByvalsonTM (Nebivolol/Valsartan) Tablets

Applicant: Forest Laboratories, Inc.

**Rao V. Kambhampati, Ph.D.
ONDQA/DNDQA I/Branch I**

**Quality (CMC) Review
For Division of Cardiology and Renal Products (DCRP)**

Chemistry Review Data Sheet

1. NDA# **206302**
2. REVIEW #: 1
3. REVIEW DATE: 10-24-2014
4. REVIEWER: Rao V. Kambhampati, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

None

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Original 0000	2/24/14
Amendment 0001	2/26/14
Amendment 0003	5/15/14
Amendment 0004	5/16/14
Amendment 0005	6/11/14
Amendment 0006	6/12/14
Amendment 0011	7/3/14
Amendment 0015	8/8/14
Amendment 0019	8/28/14

7. NAME & ADDRESS OF APPLICANT:

Name:	Forest Laboratories, Inc.
Address:	Harborside Financial Center Plaza V, Suite 1900 Jersey City, NJ 07311

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Byvalson™ Tablets
- b) Non-Proprietary Name (USAN): nebivolol/valsartan tablets
- c) Code Name/#: R065824 (nebivolol); R067555 (nebivolol HCl); VN (valsartan)

- Chem. Type: 4 (new combination)
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: NDA (21 CFR 314.50), 505 (b)(2)

10. PHARMACOL. CATEGORY: Anti-hypertensive [beta adrenergic blocker (nebivolol) and angiotensin II receptor blocker (valsartan)]

11. DOSAGE FORM: Tablets (Immediate Release, Fixed Dose Combination)

12. STRENGTH/POTENCY: 5 mg/80 mg; 5 mg/160 mg; 10 mg/160 mg; 10 mg/320 mg; and 20 mg/320 mg of nebivolol and valsartan, respectively per tablet.

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

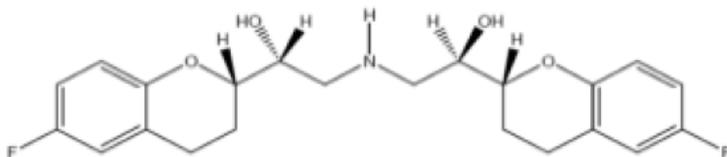
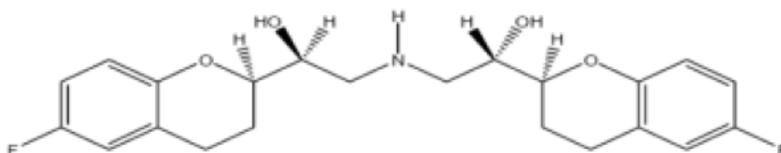
Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

i) Nebivolol Hydrochloride:

(±)-[2R*[R*[R*(S*)]]]-α,α'-[iminobis(methylene)]bis[6- fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol] hydrochloride

Nebivolol HCl has 4 stereogenic carbon centers (ie, asymmetric or chiral carbon atoms). Because of the presence of 4 stereogenic centers in the nebivolol molecule, 10 different stereoisomers (ie, meso compounds, enantiomers, and diastereomers) can be formed for this compound. However, the drug substance that is used in this product is the racemate of the enantiomeric pair (SRRR)-nebivolol (ie, *d*-nebivolol) and (RSSS)-nebivolol (i.e., *l*-nebivolol). The structural formulas (free bases) of the 2 enantiomers are provided below:

Figure 1.2.1-1. (SRRR)- or *d*-NebivololFigure 1.2.1-2. (RSSS)- or *l*-Nebivolol

$C_{22}H_{25}F_2NO_4 \cdot HCl$
M.W. = 441.90 g/mol

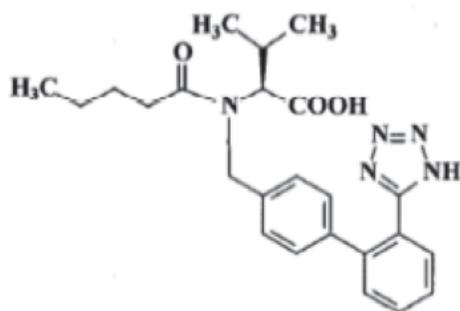
ii) Valsartan:

N-(1-oxopentyl)-N-[[2'-(1H-tetrazol-5-yl)-(1,1'-biphenyl)-4-yl] methyl]-(L)-valine
(OR)

N-(p-(O-1H-Tetrazol-5-ylphenyl)benzyl)-Nvaleryl-(L)-valine
(OR)

N-pentanoyl-N-[2' - (1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-(L)-valine

Structural Formula:



$C_{24}H_{29}N_5O_3$
M.W. = 435.52 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

M. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	9/16/13, filed in DARRTS (9/18/13) and 10/23/14 filed in DARRTS.
	II			1	Adequate	9/24/14, filed in DARRTS (10/8/14)

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under “Comments”)

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	109771	Clinical development of the drug; Sponsor: Forest Laboratories
NDA	20665	Diovan (valsartan) capsules, 80 and 160 mg; Applicant: Novartis
NDA	21283	Diovan (valsartan) tablets, 80, 160, and 320 mg tablets, Applicant: Novartis
NDA	21742	Bystolic (nebivolol hydrochloride), Applicant: Forest Laboratories

STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	4/15/14	R. Safaai-Jazi, OC
ONDQA Biopharm	Dissolution method is pending.	10/23/14	Houda Mahayni, Ph.D.
LNC (ONDQA) for Established Name	Not applicable. USAN names available.	10/23/14	Rao Kambhampati, Ph.D.
Methods Validation	Not necessary per current ONDQA Policy	10/23/14	Rao Kambhampati, Ph.D.
Package Insert and Medication Guide	DCRP decided not to review during this review cycle	10/23/14	Rao Kambhampati, Ph.D.
Container labels, carton labeling, and prescribing information	Recommended to increase prominence and readability.	10/22/14	Grace Jones, Pharm. D., (DMEPA/OSE). Review filed in DARRTS .
Proprietary name	Byvalson TM acceptable	8/22/14	Kellie A. Taylor, Pharm. D, MPH, (OMEPRM/OSE); Reviewed by Jean C. Olumba, filed in DARRTS (8/12/14)
EA	Acceptable based on EIC.	10/23/14	Rao Kambhampati, PhD
Product Quality Microbiology	Microbial limits method acceptable.	5/28/14	Erika Pfeiler, NDMS, OPS; Review filed in DARRTS.

The Chemistry Review for NDA 206302

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the Chemistry, Manufacturing, and Controls (CMC) review stand point, the NDA# 206302 for Nebivolol/Valsartan fixed dose combination tablets is recommended for approval provided the revised labeling and labels, when reviewed are acceptable to the DCRP and other relevant divisions and the dissolution method is acceptable to ONDQA Biopharm reviewer.

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

Not applicable.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substances:

The drug product contains two active pharmaceutical ingredients, nebivolol hydrochloride and valsartan. Both the drug substances are currently used in monotherapy drug products. The applicant cross-referenced the CMC information to the corresponding DMFs # (b) (4) (nebivolol hydrochloride) and (b) (4) (valsartan) and provided LOAs from the DMF Holders, which are acceptable. Nebivolol HCl is currently used in the approved drug product, Bystolic tablets, which is marketed by Forest Laboratories Inc. under NDA 21742. Valsartan is used in two currently approved drug products, Diovan capsules and Diovan tablets, both of which are marketed by Novartis under NDA 20665 and NDA 21283, respectively.

Drug Product:

The drug product is a fixed dose combination (FDC) immediate release tablet, which is manufactured in five strengths, 5 mg/80 mg; 5 mg/ 160 mg; 10 mg/160 mg; 10 mg/320 mg; and 20 mg/320 mg of nebivolol and valsartan per tablet. (b) (4)

The tablets

(b) (4)

are film coated with Opadry II film coating

(b) (4)

The tablets are manufactured at Forest Laboratories Ireland Ltd., Dublin, Ireland. The manufacturing process involves following main steps:

(b) (4)

The specifications (with limits) for tablets included the following: description; identification A for nebivolol and valsartan; identification B for nebivolol and valsartan; $(b) (4)$ content uniformity (USP <905>) for nebivolol and valsartan; assay for nebivolol ($(b) (4)$ % free base) and valsartan ($(b) (4)$ %); dissolution for nebivolol and valsartan (refer to the biopharmaceutics review for specifications); degradation products [nebivolol unspecified each ($\leq (b) (4)$ %); nebivolol total ($\leq (b) (4)$ %); valsartan unspecified each ($\leq (b) (4)$ %); and valsartan total ($\leq (b) (4)$ %)]; and microbial limits (USP/NF). The tablet specification including the tests and acceptance criteria are acceptable. Description and method validation reports were provided for all the non-compendial analytical methods and they are acceptable. Batch analysis information and results were provided for three NDA registration batches (for each strength) which were manufactured at commercial scale and packaged in the proposed container and closures. It was shown that the tablets can be manufactured with consistent quality and purity.

The primary packaging components of container closure system used for commercial distribution of drug product tablets are HDPE bottles

(b) (4)

The bottles are $(b) (4)$ HDPE

(b) (4)

Supporting documentation for the bottles and caps including the manufacturer LOAs to reference the DMF and those of materials of construction, manufacturer Certificates of Compliance and commercial release specifications were provided in the NDA.

Stability study results were provided for all bottle (b) (4) packaged tablets. On the basis of 18 months real time long-term and 6 months accelerated stability data and regression analysis, the applicant stated that the drug product would be stable for 24 months under long-term conditions. The applicant proposed expiration dating period of 24 months for (b) (4) the drug product (b) (4)

(b) (4)

At the time of this review, the biopharmaceutics reviewer is still considering modifications to the dissolution method and the specification acceptance limits. Therefore, an expiration dating period of 24 months is granted (b) (4)

(b) (4)

C. Description of How the Drug Product is Intended to be Used

Nebivolol/valsartan Tablets are indicated for the treatment of hypertension, to lower blood pressure. The recommended starting dose is 5/80 mg (b) (4) taken orally once daily. (b) (4)

(b) (4) Nebivolol/valsartan Tablets are supplied in the following strengths and package configurations:

Tablet Strength	Package Configuration	NDC #	Tablet Color/Shape	Tablet Marking
5/80 mg	Bottle of 30	(b) (4)	Purple / capsule shaped	FL1, on one side
	Bottle of 90			
	10 x 10 Unit Dose	0456-1450-63		
5/160 mg	(b) (4)			
10/160 mg				
10/320 mg				
20/320 mg				

The tablets are recommended to be stored at 20° to 25°C (68° to 77°F) [see USP for Controlled Room Temperature] and dispensed in a tightly closed (b) (4) container as defined in the USP (b) (4)

D. Basis for Approvability or Not-Approval Recommendation

The applicant provided adequate chemistry, manufacturing, and controls (CMC) information for the drug substance and drug product. The applicant satisfactorily addressed all the deficiencies that were communicated during the review. The established names, nebivolol hydrochloride and valsartan, are USAN names and they are acceptable. The tradename, Byvalson™ is acceptable to DMEPA and other relevant divisions. The microbial limits test methods are acceptable from the product microbiology reviewer stand point. All the facilities are acceptable to the Office of Compliance. DCRP decided not to review labeling and labels during this review cycle. From the CMC stand point the NDA is recommended for approval provided revised labeling and labels, when reviewed are acceptable to DCRP and other relevant divisions. Finally, the applicant proposed protocol to submit new drug substance manufacturers as a changes being effected-30 rather than a prior approval supplement. The applicant should be advised the following regarding their proposed protocol in the approval letter:

“For the comparability protocol in section 3.2.R to change drug substance manufacturing sites, the data set, test methods, and acceptance criteria you intend to send in your CBE-30 appears appropriate. However, because you have not yet identified the potential manufacturing sites, we cannot comment as to whether the supplement would be filed as a CBE-30 supplement. When you submit your CBE-30 to change or add drug substance manufacturers, the supplement will be filed as a CBE-30 only if the proposed site is cGMP compliant for the intended operation at the time of submission. We ask that you confirm your understanding of this agreement regarding your comparability protocol. Please refer to the ‘Guidance for Industry: Changes to an Approved NDA or ANDA,’ section VI, for further information regarding filing categories for manufacturing facility change supplements.

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm077097.pdf>”

III. Administrative

A. Reviewer’s Signature

Rao V. Kambhampati, Ph.D.

B. Endorsement Block

Primary Reviewer/Date: Rao V. Kambhampati, Ph.D.

Executive Summary Section

NDA 206302

Senior Chemist/ONDQA/DNDQA I/Branch I

Secondary Reviewer/Date: Olen Stephens, Ph.D.
Acting Branch Chief/ONDQA/DNDQA I/Branch I



CHEMISTRY REVIEW



Executive Summary Section

NDA 206302

Initial Quality Assessment of Product Quality Risk:

Product attribute/CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment
Assay, Stability	(b) (4)	3 Both DS	2	Release 1	6 Both DS	(b) (4)
				Stability 3	18 Both DS	
				Physical stability (solid state)	3 (neb) 4 (val)	
Content uniformity	(b) (4)	3 (neb) 2 (val)	3 (neb) 2(val)	4 (neb)	36 (neb)	(b) (4)
				4 (val)	16 (val)	
Microbial limits	(b) (4)	1	2	3	6	Microbiology review done –acceptable
Dissolution	(b) (4)	4	2	4	32	(b) (4)
BCS Class 2 (neb) and 4 (val)	(b) (4)	3	2	4	24	(b) (4)

(b) (4)



CHEMISTRY REVIEW



Executive Summary Section

NDA 206302

Final Quality Assessment of Product Quality Risk:

From Initial Quality Assessment			Review Assessment	
Product attribute/CQA	Factors that can impact the CQA	Probability (O)	Risk Evaluation	Lifecycle Considerations/Comment
Assay, Stability	(b) (4)	3 Both DS	Acceptable	Type of container can have impact on the stability of drug product tablets.
Physical stability (solid state)		3 (neb) 4 (val)	Acceptable (neb) Acceptable (val)	None at this time
Content uniformity		3 (neb)	Acceptable (neb)	(b) (4)
		2 (val)	Acceptable (val)	
Microbial limits		1	Acceptable	None at this time
Dissolution BCS Class 2 (neb) and 4 (val)		4	Acceptable	(b) (4)



CHEMISTRY REVIEW



Executive Summary Section

NDA 206302

(b) (4)	(b) (4)	3	Acceptable	None at this time
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**II. Review of Common Technical Document-Quality (Ctd-Q) Module 1**

- 1.14 Labeling & Package Insert:** The proposed package inserts, medication guide, and container and carton labels contained required CMC related information. However, the clinical division (DCRP) decided not to review the labeling during this review cycle but DMEPA (OSE) reviewed the container labels, carton labeling, and Prescribing Information for Byvalson from their stand point and suggested to increase the prominence and readability of important information to promote safe use of the product.

List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis, along with postmarket medication error data, DMEPA reviewed the following Byvalson labels and labeling submitted by Forest Laboratories Inc. on July 3, 2014.

Container Label

Professional Sample Container, Carton, Tray Labeling

Professional Sample Container, Carton, Tray Labeling (Early Sample)

(b) (4)

(b) (4)

7 Pages have been Withheld in Full as B4 (CCI/TS)
immediately following this page

1. Add the unit of measurement immediately following all numbers that designate the strength throughout the PI. For example, revise the strength [REDACTED] (b) (4) to "5 mg/80 mg."

DMEPA reviewer made the following recommendations to the Applicant:

A. Container Labels and Carton labeling – including Container Label; Professional Sample Container, Carton, Tray Labeling; Professional Sample Container, Carton, Tray Labeling (Early Sample) [REDACTED] (b) (4)

1. Revise the presentation of the established name so it is printed in letters that are at least half as large as the letters comprising the proprietary name. The established name should have a prominence commensurate with the prominence with such proprietary name, taking into account typography, layout, contrast and other printing features in accordance with 21 CFR 201.10(g)(2).

2. Revise the strength expression to include the unit of measurement immediately following all numbers on the principal display panel and the side panel. For example, revise the statement [REDACTED] (b) (4)

3. Revise the color scheme for the 5 mg/80 mg strength of Byvalson to improve readability and provide sufficient color contrast between the two colors. The currently proposed color scheme of white text on [REDACTED] (b) (4) highlight compromises readability [REDACTED] (b) (4)

4. Relocate the net quantity statement to the bottom of the principal display panel (PDP) [REDACTED] (b) (4) and away from the strength statement for all applicable container labels and carton labeling [REDACTED] (b) (4)

5. [REDACTED] (b) (4)

Overall Comments: Initially the applicant proposed [REDACTED] (b) (4) as the tradename, however, it was determined to be not acceptable to DMEPA. Later, the applicant submitted Byvalson as the tradename, which was found to be acceptable to DMEPA and all other relevant divisions. The applicant later submitted container and carton labels with Byvalson as tradename. In general

these labels contained required CMC related information but they could be further improved by incorporating the recommendations made by DMEPA. Therefore, the applicant needs to make the recommended changes in the final labels.

1.12.14 Environmental Assessment or Claim of Categorical Exclusion: Forest Laboratories, Inc. claimed a categorical exclusion from the requirements to prepare an Environmental Assessment for this NDA related to its combination product, Nebivolol/Valsartan (b) (4). The applicant stated that the Agency's approval of the application increases the use of the active moieties nebivolol and valsartan, but the estimated concentration of the substances at the point of entry into the aquatic environment will be below 1 part per billion (ppb). The calculated maximum Expected Introduction Concentrations (EIC) from direct use of nebivolol/valsartan tablets entering into the aquatic environment are (b) (4) and (b) (4) ppb for nebivolol and valsartan, respectively, and is unlikely to have a significant affect on the environment.

The estimated concentration of nebivolol and valsartan at the point of entry into the aquatic environment was calculated in accordance to the FDA *Guidance for Industry: Environmental Assessment of Human Drug and Biologics Application* dated July 1998. The concentration was estimated using the highest quantity (in kg) of the active moiety expected to be produced for all strengths for direct use in highest forecast year within the next five years. The calculations of the Expected Introduction Concentration (EIC) of the active moiety into the aquatic environment are provided in Table 1.12.14-1 and Table 1.12.14-2 of the NDA, respectively.

Comments: Acceptable on the basis of the EIC calculation submitted in the NDA.

Establishment Evaluation

A copy of the Establish Evaluation Report is provided below:



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

NDA 206302

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST DETAIL REPORT

Application:	NDA 206302/000	Action Goal:	
Stamp Date:	24-FEB-2014	District Goal:	25-OCT-2014
Regulatory:	24-DEC-2014		
Applicant:	FOREST LABS INC PLAZA V STE 1900 JERSEY CITY, NJ 07311	Brand Name:	NEBIVOLOL AND VALSARTAN
		Estab. Name:	
		Generic Name:	NEBIVOLOL AND VALSARTAN
Priority:	4	Product Number; Dosage Form; Ingredient; Strengths	
Org. Code:	110	005; TABLET; NEBIVOLOL HYDROCHLORIDE; 5.45MG 005; TABLET; VALSARTAN; 80MG	(b) (4)

Application Comment:

FDA Contacts:	R. KAMBHAMPATI	Prod Qual Reviewer	(HFD-830)	3017961382
	Y. KNIGHT	Product Quality PM		3017962133
	M. MONTELEONE	Regulatory Project Mgr	(HFD-110)	3017961952
	K. SRINIVASACHAR	Team Leader		3017961760

Overall Recommendation:	ACCEPTABLE	on 15-APR-2014	by R. SAFAAI-JAZI	()	3017964463
	PENDING	on 27-MAR-2014	by EES_PROD		
	PENDING	on 25-MAR-2014	by EES_PROD		

Establishment: CFN: (b) (4) FEI: (b) (4) (b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE PACKAGER

Establishment Comment: DRUG PRODUCT PACKAGING (BOTTLE (b) (4)) (on 13-MAR-2014 by Y. KNIGHT () 3017962133)

Profile: TABLETS, PROMPT RELEASE **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					
SUBMITTED TO OC	25-MAR-2014				KNIGHTY
OC RECOMMENDATION	25-MAR-2014			ACCEPTABLE	SAFAAIJAZIR



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

NDA 206302

Establishment: CFN: [REDACTED] FEI: (b) (4)

DMF No: [REDACTED] AADA: [REDACTED]

- Responsibilities:
- DRUG SUBSTANCE MANUFACTURER
 - DRUG SUBSTANCE PACKAGER
 - DRUG SUBSTANCE RELEASE TESTER
 - DRUG SUBSTANCE STABILITY TESTER

Establishment Comment: MANUFACTURING, PACKAGING, RELEASE, AND STABILITY TESTING OF VALSARTAN API (on 24-MAR-2014 by Y. KNIGHT (J) 3017962133)

Profile: [REDACTED] (b) (4) OAI Status: NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
SUBMITTED TO OC					
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					

SUBMITTED TO OC	25-MAR-2014				KNIGHTY
OC RECOMMENDATION	25-MAR-2014			ACCEPTABLE	SAFAAJAZIR

Establishment: CFN: (b) (4) FEI: (b) (4)

DMF No: [REDACTED] AADA: [REDACTED]

- Responsibilities:
- FINISHED DOSAGE OTHER TESTER

Establishment Comment: MICROBIAL TESTING (on 13-MAR-2014 by Y. KNIGHT (J) 3017962133)

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
SUBMITTED TO OC					
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					

SUBMITTED TO OC	25-MAR-2014				KNIGHTY
OC RECOMMENDATION	25-MAR-2014			ACCEPTABLE	SAFAAJAZIR



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

NDA 206302

Establishment: CFN: (b) (4) FEI: (b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

Establishment Comment: (b) (4) MICROBIAL TESTING (on 13-MAR-2014 by Y. KNIGHT () 3017962133)

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					

SUBMITTED TO OC	25-MAR-2014				KNIGHTY
OC RECOMMENDATION	25-MAR-2014			ACCEPTABLE	SAFAAJAZIR

Establishment: CFN: 2436921 FEI: 1000521508

FOREST LABORATORIES INC

220 SEA LANE
FARMINGDALE, NY 117353900

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER

FINISHED DOSAGE STABILITY TESTER

Establishment Comment: DRUG PRODUCT RELEASE AND STABILITY TESTING (on 05-MAR-2014 by Y. KNIGHT () 3017962133)

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					

SUBMITTED TO OC	25-MAR-2014				KNIGHTY
OC RECOMMENDATION	25-MAR-2014			ACCEPTABLE	SAFAAJAZIR



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

NDA 206302

Establishment: CFN: 9816660 FEI: 3002806993
 FOREST LABORATORIES IRELAND, LTD.
 CLONSHAUGH BUSINESS AND TECHNOLOGY PARK
 DUBLIN 17, CLONSHAUGH, IRELAND

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER
 FINISHED DOSAGE RELEASE TESTER
 FINISHED DOSAGE STABILITY TESTER

Establishment Comment: DRUG PRODUCT MANUFACTURING, RELEASE AND STABILITY TESTING
 INACTIVE INGREDIENTS RELEASE TESTING (on 05-MAR-2014 by Y. KNIGHT () 3017962133)

Profile: TABLETS, PROMPT RELEASE OAI Status: NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					

SUBMITTED TO OC	25-MAR-2014				KNIGHTY
SUBMITTED TO DO PDUFA GOAL DATE: 24-DEC-2014	25-MAR-2014	GMP Inspection			SAFAAIJAZIR
DO RECOMMENDATION [REDACTED]	11-APR-2014			ACCEPTABLE	PHILPYE
OC RECOMMENDATION	15-APR-2014			ACCEPTABLE	SAFAAIJAZIR

Establishment: CFN: 1523957 FEI: 1523957
 FOREST PHARMACEUTICALS INC
 5000 BROTHERTON RD
 CINCINNATI, OH 45209

DMF No: AADA:

Responsibilities: FINISHED DOSAGE PACKAGER

Establishment Comment: DRUG PRODUCT PACKAGING (BOTTLES (b) (4)) (on 13-MAR-2014 by Y. KNIGHT () 3017962133)

Profile: TABLETS, PROMPT RELEASE OAI Status: NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					

SUBMITTED TO OC	25-MAR-2014				KNIGHTY
OC RECOMMENDATION	25-MAR-2014			ACCEPTABLE	SAFAAIJAZIR



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

NDA 206302

Establishment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE STABILITY TESTER
(b) (4)

Establishment Comment:

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					

SUBMITTED TO OC	28-MAR-2014				KNIGHTY
OC RECOMMENDATION	01-APR-2014			ACCEPTABLE	SAFAAJAZIR

Establishment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE RELEASE TESTER

Establishment Comment: MANUFACTURING, PACKAGING AND RELEASE TESTING (on 05-MAR-2014 by Y. KNIGHT () 3017962133)

Profile: (b) (4) OAI Status: NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					

SUBMITTED TO OC	25-MAR-2014				KNIGHTY
OC RECOMMENDATION	25-MAR-2014			ACCEPTABLE	SAFAAJAZIR

Chemistry Assessment Section

NDA 206302

Establishment: CFN: [REDACTED] FEI: (b) (4)
 [REDACTED] (b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE STABILITY TESTER

Establishment Comment:

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
<u>Comment</u>					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
<u>Reason</u>					

SUBMITTED TO OC	25-MAR-2014				KNIGHTY
OC RECOMMENDATION	25-MAR-2014			ACCEPTABLE	SAFAAIJAZIR

Establishment: CFN: (b) (4) FEI: (b) (4)
 [REDACTED] (b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

Establishment Comment: [REDACTED] (b) (4) (on 03-APR-2014 by Y. KNIGHT () 3017962133)

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
<u>Comment</u>					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
<u>Reason</u>					

SUBMITTED TO OC	03-APR-2014				KNIGHTY
OC RECOMMENDATION	03-APR-2014			ACCEPTABLE	IYERS

Comments: Acceptable. The initial manufacturing assessment (CGMP/Facilities) and filing review (IMA) was filed in DARRTS by Vibhakar Shah, Ph.D. on 9/19/14, in which he determined that the NDA is filable from OC perspective. All the facilities that are involved in the manufacturing and testing of the drug substances and drug product were determined to be acceptable by the Office of Compliance (OC) either on the basis of their file review or inspection. The OC issued an Overall Recommendation of Acceptable for this NDA on 4/15/14 by R. Safaai-Jazi and later it was again confirmed by Vibhakar Shah (e-mail 7/21/14).

Protocol:

Chemistry Assessment Section

NDA 206302

The applicant submitted a comparability protocol to demonstrate the equivalence of nebivolol hydrochloride and valsartan drug substance manufactured at alternate sites and/or manufacturers (PRD-PR-ANL-01244).

The applicant stated that the objective of the comparability protocol is to present the overall plan and commitments that will be undertaken by the sponsor (b) (4)

 (b) (4)

(b) (4)

Comments: The applicant should be informed that the protocol as submitted is acceptable with the following proviso:

For the comparability protocol in section 3.2.R to change drug substance manufacturing sites, the data set, test methods, and acceptance criteria you intend to send in your CBE-30 appears appropriate. However, because you have not yet identified the potential manufacturing sites, we cannot comment as to whether the supplement would be filed as a CBE-30 supplement. When you submit your CBE-30 to change or add drug substance manufacturers, the supplement will be filed as a CBE-30 only if the proposed site is cGMP compliant for the intended operation at the time of submission. We ask that you confirm your understanding of this agreement regarding your comparability protocol. Please refer to the 'Guidance for Industry: Changes to an Approved NDA or ANDA,' section VI, for further information regarding filing categories for manufacturing facility change supplements.

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm077097.pdf>

III. List Of Deficiencies Communicated

The following CMC comments and recommendations were communicated to the applicant in the letter dated August 1, 2014:

1. Please provide a master batch record or a proposed master batch record. If the submitted executed batch records are identical to the master batch record, provide a statement.

Chemistry Assessment Section

NDA 206302

2. We noticed [REDACTED] ^{(b) (4)} at the time of lot release. In order for us to aid in the assignment of shelf-life, please provide regression analysis of the dissolution study results and total impurities content results of the drug product stability lots.
3. [REDACTED] ^{(b) (4)}
[REDACTED] This study will elucidate potential drug product quality risks related to the different container closure sources.
4. Provide updated real time stability study results of the NDA registration batches.

Comments: The applicant satisfactorily addressed the above comments in the Amendment dated 8/8/14 and the responses are discussed in the appropriate sections of this NDA. No other CMC issues are pending at present.

Digitally signed by Rao V. Kambhampati -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People, 0.9.2342.19200300.100.1.1=1300073803,
cn=Rao V. Kambhampati -A
Date: 2014.10.24 16:13:13 -04'00'

Olen Stephens -A
Digitally signed by Olen Stephens -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,
cn=Olen Stephens -A, 0.9.2342.19200300.100.1.1=2000558826
Date: 2014.10.24 16:15:57 -04'00'

BIOPHARMACEUTICS REVIEW
Office of New Drug Quality Assessment

Application No.:	NDA 206-302	Reviewer:	
Division:	DCRP	Houda Mahayni, Ph.D.	
Applicant:	Forest Research Institute, Inc.	Team Leader: Angelica Dorantes, Ph.D.	
Trade Name:	Byvalson™	Acting Supervisor: Paul Seo, Ph.D.	
Generic Name:	Nebivolol/Valsartan Fixed Dose Combination	Date Assigned:	2/24/2014
Indication:	For the treatment of hypertension as add-on therapy, replacement therapy, and initial therapy	Date of Review:	10/15/2014
Formulation/strength	Tablets (5/80, 5/160, 10/160, 10/320, and 20/320 mg)		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Submission Dates	GRMP Date	PDUFA Date
2/24/2014 8/8/2014 (partial response to biopharm IR dated 8/1/2014) 8/28/2014 (complete response to biopharm IR dated 8/1/2014)	10/24/2014	12/24/2014

Type of Submission:	505 (b) (2)
Key review points	<ol style="list-style-type: none"> 1. Dissolution method and acceptance criteria 2. (b) (4) 3. One Bioequivalence study

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2. Is there any information on BCS classification? What claim did the Applicant make based on BCS classification? What data are available to support this claim?	
B) DISSOLUTION INFORMATION	14
B.1. DISSOLUTION METHOD	
3. What is the proposed dissolution method?	
4. What data are provided to support the adequacy of the proposed dissolution method (e.g. medium, apparatus selection, etc.)?	
5. What information is available to support the robustness (e.g. linearity, accuracy, etc.) of the dissolution methodology?	
6. What data are available to support the discriminating power of the method?	
7. Is the proposed dissolution method biorelevant? What data are available to support this claim?	
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9. What are the proposed dissolution acceptance criteria for this product?	
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12. Are mean (n=12) dissolution profile data used for the setting of the acceptance criteria?
13. Are the acceptance criteria acceptable? If not, what are the recommended acceptance criteria?

C) DRUG PRODUCT FORMULATION DEVELOPMENT and BRIDGING ACROSS PHASES 28

14. What is the composition of the formulation of the proposed product?
15. What are the highlights of the drug product formulation development?

16. Are all the strengths evaluated in the pivotal clinical trials? If not, what data are available to support the approval of lower strengths?

17. Are there any manufacturing changes implemented (e.g. formulation changes, process changes, site change, etc.) to the clinical trial formulation? What information is available to support these changes?

18. Is the formulation of the clinical product the same formulation of the to-be-marketed product? If not, what information is available to support the formulation changes?

19. Is the manufacturing site the same for the clinical and to-be-marketed products? If not, what information is available to support the new site?

D) DISSOLUTION APPLICATIONS 35

D.1 BIOWAIVERS

20. Is there a waiver request of in vivo BA or BE data (Biowaiver)? If yes, what is/are the purpose/s of the biowaiver request/s? What data support the biowaiver request/s? Is the biowaiver request acceptable?

21. Is there any IVIVR or IVIVC information submitted? What is the regulatory application of the IVIVR/IVIVC in the submission? What data are provided to support the acceptability of the IVIVR or IVIVC model?

D.2 SURROGATES IN LIEU OF DISSOLUTION 45

22. Are there any manufacturing parameters (e.g. disintegration, drug substance particle size, etc.) being proposed as surrogates in lieu of dissolution testing? What data are available to support the approval of the proposed surrogate test?

D.3 DISSOLUTION AND QBD 45

23. Does the application contain QbD elements? If yes, is dissolution identified as a CQA for defining design space?

24. Was dissolution included in the DoE? What raw materials and process variables are identified as having an impact on dissolution? What is the risk assessment performed to evaluate the criticality of dissolution?

25. What biopharmaceutics information is available to support the clinical relevance of the proposed design space?
26. Is there any dissolution model information submitted as part of QbD implementation? What is the regulatory application of the dissolution model in the submission? What data are provided to support the acceptability of the dissolution model?

E) BIOEQUIVALENCE STUDY: NAC-PK-07

46

27. Is the bioequivalence study design appropriate?
28. Does the bioequivalence study demonstrate bioequivalence between treatments?
29. Is the bioanalytical method validated?
30. Is the information/data provided support the Applicant's conclusion of bioequivalence between the two treatments?
31. Is the bioequivalence study adequate to support approval?

D) SUMMARY OF BIOPHARMACEUTICS FINDINGS

Submission:

The Applicant submitted this NDA for nebivolol/valsartan fixed-dose combination (FDC) tablets 5/80 mg, 5/160 mg, 10/160 mg, 10/320 mg, and 20/320 mg, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetics Act. The FDC contains two approved drugs, nebivolol, a β -adrenergic receptor blocker, and valsartan, an angiotensin II type 1 receptor blocker. The Applicant is relying on FDA's previous findings of safety and effectiveness for the listed drug Diovan (valsartan) based on NDA 20-665 for 80 and 160 mg oral capsules and NDA 21-283 for 80, 160, and 320 mg oral tablets, both submitted by Novartis Pharmaceuticals Corporation, and on its own approved NDA (NDA 21-742) for Bystolic (nebivolol hydrochloride). In addition, the Applicant performed bioequivalence study between the FDC 20/320 mg and the coadministration of the individual component treatments in Study NAC-PK-05. This study was reviewed and found acceptable by the Office of Clinical Pharmacology (See Dr. Bilal S Abu Asal's reviews in DARRTS dated 8/15/2014 and 8/4/2014).

The proposed indication for the nebivolol/valsartan FDC is the treatment of hypertension as add-on therapy, replacement therapy, and initial therapy. The recommended starting dose for initial therapy is 5/80 mg, or 5/160 mg, taken orally once daily. The dosage may be increased after 2 to 4 weeks of therapy at each step up to a maximum recommended dose of 20/320 mg.

The Applicant developed (b) (4) immediate release, FDC tablet containing both nebivolol and valsartan. (b) (4)



The nebivolol/valsartan FDC clinical development program consisted of 6 clinical pharmacology and biopharmaceutical studies in healthy subjects and 2 Phase 3 studies in patients with stage 1 or 2 essential hypertension. The 2 Phase 3 studies were: an 8-week, double-blind study (NAC-MD-01), which assessed efficacy and safety of the FDC; and a 52-week, open-label study (NAC-MD-02), which assessed long-term safety/tolerability of the free-tablet combination of nebivolol and valsartan, and additionally measured BP reductions.

The nebivolol/valsartan clinical studies were conducted with different formulations of the following strengths of fixed-dose combinations of nebivolol/valsartan tablets: 5/80 mg, 5/160 mg, 10/160 mg, 10/320 mg, and 20/320 mg. (b) (4)



(b) (4) The (b) (4) formulation was used in pivotal efficacy trial (NAC-MD-01) (b) (4)

(b) (4)

(b) (4)

Review:

This Biopharmaceutics review focuses on the evaluation of:

- 1) Proposed dissolution method and acceptance criteria,
- 2) Data supporting the acceptability (b) (4) and
- 3) Data supporting the acceptability of the bioequivalence study (NAC-PK-07).

1) Dissolution Method and Acceptance Criteria:

The Applicant proposed the following dissolution method and acceptance criteria (b) (4)

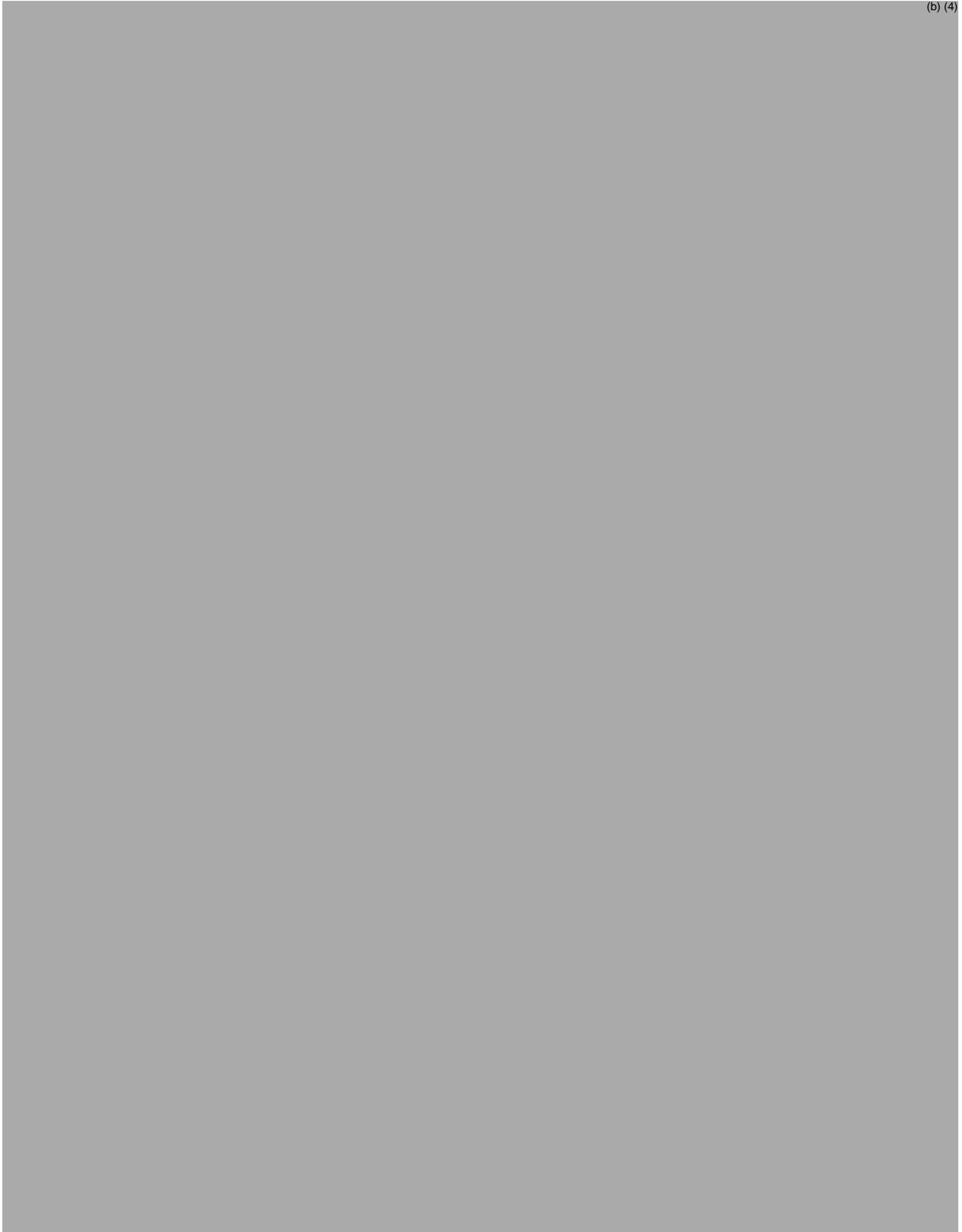
(b) (4)

USP Apparatus	Paddle Rotation	Medium Volume	Temperature/ Medium	Acceptance Criteria
USP < 711 > Apparatus I (baskets)	100 rpm	900mL	Phosphate Buffer, pH 6.8 with 0.5% SDS at 37°C	Nebivolol: (b) (4)% (Q) at 30 minutes Valsartan: (b) (4)% (Q) at 30 minutes

The proposed dissolution method is found acceptable. The proposed acceptance criteria is found acceptable for nebivolol, but not for valsartan. The dissolution data generated on the clinical batches and the registration stability batches support the acceptance criterion of NLT (b) (4)% (Q) at 30 minutes for valsartan. Therefore, the Applicant will be requested

to revise the dissolution acceptance criterion of valsartan from (b) (4) % (Q) at 30 minutes to (b) (4) % (Q) at 30 minutes and update the specification table.

(b) (4)



4) Risk Evaluation

Risk Assessment Table

Initial Risk Assessment			Final Risk Assessment		
Product attribute/CQA	Factors that can impact the CQA	Risk Ranking*	Risk Mitigation approach	Risk Evaluation	Lifecycle Considerations/Comments**
Dissolution	<p>None identified</p> <p>The Applicant (b) (4) provide acceptable dissolution profile. Also, the Applicant addressed the solubility challenge of valsartan and nebivolol (b) (4) (b) (4)</p>	Low	<p>None</p> <p>(b) (4)</p>	Acceptable	The dissolution method is acceptable. The proposed acceptance criteria are adequate for nebivolol, but not for valsartan to control the quality of the drug product.

*Risk ranking applies to product attribute/CQA

**For example, post marketing commitment, knowledge management post approval, etc.

II) RECOMMENDATION

At this time of the review process, critical information needed to complete this review is lacking and therefore at the GRMP timeline the Biopharmaceutics recommendation on the approvability of NDA 206-302 for Byvalson™ (Nebivolol/Valsartan) FDC Tablets is PENDING.

The following comments and requests for information need to be addressed by the Applicant:

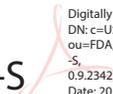
1. The proposed dissolution acceptance criterion of NLT (b) (4)% (Q) at 30 minutes for valsartan is not acceptable. The dissolution data generated on the clinical batches and the registration stability batches fully support an acceptance criterion of NLT (b) (4)% (Q) at 30 minutes for valsartan. Therefore, implement this criterion for valsartan and submit an updated specification table for your FDC product.

2. (b) (4)



Houda Mahayni, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Houda
Mahayni -S



Digitally signed by Houda Mahayni -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Houda Mahayni
-S,
0.9.2342.19200300.100.1.1=1300071188
Date: 2014.10.24 21:50:01 -04'00'

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

Angelica
Dorantes -S



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cn=Angelica Dorantes -S
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III) BIOPHARMACEUTICS ASSESSMENT-QUESTION BASED REVIEW

A) GENERAL ATTRIBUTES

1. What are the highlights of the chemistry and physico-chemical properties of the drug substance (e.g. solubility) and formulation of the drug product?

Table 1 and Table 2 below list the key physicochemical properties and other general information for nebivolol HCl and valsartan USP drug substances. Both drug substances exhibit pH-dependent solubility profiles. Nebivolol is a basic drug. The pKa of the amino group in nebivolol hydrochloride is 8.4; hence it exhibits low solubility at pH 6 and above and exhibits higher solubility at low pH conditions. On the other hand, valsartan is an acidic drug, which exhibits low solubility at low pH and high solubility at high pH (≥ 5).

Table 1: General Information and Physicochemical Properties for Nebivolol HCl (Source: 2.3.P)

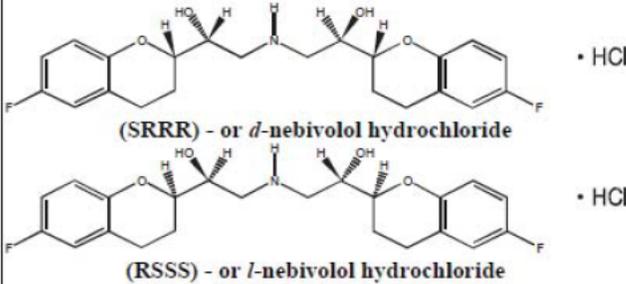
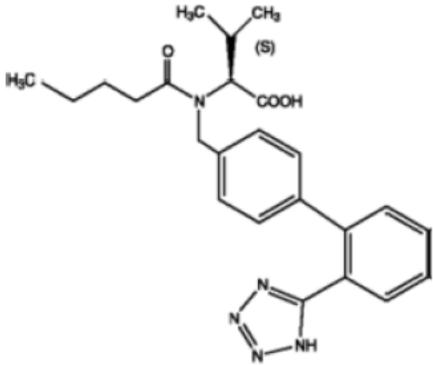
Structural formula:	 <p>(SRRR) - or <i>d</i>-nebivolol hydrochloride</p> <p>(RSSS) - or <i>l</i>-nebivolol hydrochloride</p>
Chemical name (IUPAC nomenclature):	(1 <i>RS</i> ,1' <i>RS</i>)-1,1'-[(2 <i>RS</i> ,2' <i>SR</i>)-bis(6-fluoro-3,4-dihydro-2 <i>H</i> -1-benzopyran-2-yl)]-2,2'-iminodiethanol hydrochloride
Molecular formula:	C ₂₂ H ₂₅ F ₂ NO ₄ •HCl
Relative molecular mass:	441.90 g/mol
Description:	Nebivolol hydrochloride is a racemate composed of <i>d</i> -Nebivolol and <i>l</i> -Nebivolol hydrochloride with the stereochemical designations of [SRRR]-nebivolol and [RSSS]-nebivolol, respectively. It appears as a white to almost white powder
Hygroscopicity:	Nebivolol HCl is non-hygroscopic.
BCS Classification:	Class 2 (low solubility, high permeability)
log P:	log P (b) (4) = (b) (4)
Particle size distribution:	D50: \leq (b) (4) μ m; D90: \leq (b) (4) μ m
Specific Surface Area:	\geq (b) (4) m ² /g (b) (4)
“Apparent” pKa:	pKa (amino group) = 8.4
Melting point:	The melting range is 226°C – 227°C

Table 2: General Information and Physicochemical Properties for Valsartan USP (Source: 2.3.P)

Structural formula:	
Chemical name (IUPAC nomenclature):	<i>N</i> -(1-oxopentyl)- <i>N</i> -[[2'-(1 <i>H</i> -tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]methyl]- <i>L</i> -valine.
Molecular formula:	C ₂₄ H ₂₉ N ₅ O ₃
Relative molecular mass:	435.52
Description:	Valsartan is a white or almost white fine powder
Hygroscopicity:	Valsartan is slightly hygroscopic
BCS Classification:	Class 4 (low solubility, low permeability)
"Apparent" pKa:	(b) (4)
	(b) (4)

The Applicant developed an immediate-release, FDC tablet containing both nebivolol and valsartan intended for oral administration. The proposed five strengths of nebivolol/valsartan tablets are: 5/80 mg, 5/160 mg, 10/160 mg, 10/320 mg, and 20/320 mg. (b) (4)

The drug product contains the following excipients: lactose monohydrate, microcrystalline cellulose, copovidone, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate (b) (4) talc, ferric oxide, hypromellose, polysorbate 80, and Opadry® II film coatings. The composition of the TBM formulations for nebivolol/valsartan FDC tablets (5/80 mg, 5/160 mg, 10/160 mg, 10/320 mg, 20/320 mg) is shown in Table 3 below.

Table 3: Composition of TBM Formulation for Nebivolol/Valsartan FDC Tablets (5/80 mg, 5/160 mg, 10/160 mg, 10/320 mg, 20/320 mg) (Source: drug-product-nebivolol-valsartan-tablets.pdf)

<i>Ingredients</i>	<i>Formulation Composition</i>
	(b) (4)
	(b) (4)
Lactose monohydrate, NF	(b) (4)
Microcrystalline cellulose, NF	
Copovidone, NF	
Croscarmellose sodium, NF	
Talc, USP	
Colloidal silicon dioxide, NF	
Magnesium stearate, NF	
(b) (4)	
Ferric oxide, NF	
Hypromellose (b) (4) USP	
Polysorbate 80, NF	
	(b) (4)
Opadry® II	(b) (4)
a	(b) (4)
b	(b) (4)

Nebivolol/Valsartan Tablets, 5/80 mg are capsule shaped, purple coated tablets and debossed with “FL1” on one side.



2. Is there any information on BCS classification? What claim did the Applicant make based on BCS classification? What data are available to support this claim?

According to the Applicant, Nebivolol and valsartan belong to Biopharmaceutics Classification System (BCS) Class II and IV, respectively.

The solubility data in Table 4 below shows (b) (4)

Therefore, the Applicant determined that nebivolol is a low solubility drug. The Applicant reported that the permeability of nebivolol is moderate-to-high across Caco-2 monolayers with an apparent permeability (Papp) of about (b) (4) cm/sec, as shown in Table 6 below.

The Applicant stated that the valsartan solubility data in Table 5 shows (b) (4)

therefore the Applicant classified valsartan as a low solubility drug. (b) (4)

The Applicant stated that although valsartan is classified as a BCS IV drug, it may behave like a high solubility and low permeability (BCS III) drug due to its high solubility at higher pH conditions, such as that in the intestine where most drugs are absorbed.

Valsartan exhibits a Caco-2 Papp of about (b) (4) cm/sec, as shown in Table 6, and the Applicant classified valsartan as a low permeability drug because the Papp A → B is (b) (4) cm/sec across Caco-2 monolayers.

Table 4 and Table 5 provide the pH solubility of Nebivolol and Valsartan, respectively.

Table 4: pH Solubility of Nebivolol HCl at 37° C (Source: 2.3.P)

<i>Equilibrium pH (Media)</i>	<i>Solubility (µg/mL)</i>
(b) (4)	

Table 5: pH Solubility of Valsartan at 37°C (Source: 2.3.P)

<i>Equilibrium pH (Media)</i>	<i>Solubility, µg/mL</i>
(b) (4)	

Table 6 provided the permeability of Nebivolol HCl and Valsartan across Caco-2 Monolayer.

Table 6: Permeability of Nebivolol HCl and Valsartan Across Caco-2 Monolayers (Source: 2.3.P)

<i>Drug (concentration)</i>	<i>P_{app} A→B (cm/sec)</i> <i>(×10⁻⁶ cm/s)</i>	<i>P_{app} B→A (cm/sec)</i> <i>(×10⁻⁶ cm/s)</i>	<i>P_{app} B→A/P_{app} A→B</i>
(b) (4)			

Reviewer’s Assessment: *SATISFACTORY*

(b) (4)

B) DISSOLUTION INFORMATION

B.1. DISSOLUTION METHOD

3. What is the proposed dissolution method?

The Applicant stated that the dissolution method is based on USP <711> Dissolution and Acceptance Table 1 for Immediate-Release Dosage Forms. The dissolution test parameters of the proposed dissolution method are:

Apparatus: USP I (Basket)
 Medium: 67 mM phosphate buffer solution (pH 6.8) with 0.5% SDS
 Speed: 100 rpm
 Volume: 900 mL

The chromatographic conditions of the dissolution method are provided in Table 7.

Table 7: HPLC Chromatographic Conditions for Dissolution (Source: drug –product-nebivolol-valsartan-tablets.pdf)

<i>HPLC Conditions:</i>
(b) (4)

Reviewer’s Comment: The dissolution method test parameters are acceptable. They are considered appropriate for BCS Class 2 and 4 compounds formulated as an immediate-release solid oral dosage form.

3. What data are provided to support the adequacy of the proposed dissolution method (e.g. medium, apparatus selection, etc.)?

➤ *Apparatus*

The Applicant evaluated the product in both USP Apparatus I (Baskets) (b) (4)

(b) (4)

The Applicant stated that Apparatus I (baskets) provided a more consistent release profile and was eventually chosen as the more robust option.

Table 8: Summary of Experiment for Dissolution Apparatus Screening

<i>Parameter</i>	
Strength	(b) (4)
Apparatus	
Speed of Rotation	
Bath Temperature	
Volume	
Sampling points	
Medium	

Figure 1: Comparison of USP Apparatus I (b) (4) for Nebivolol Dissolution in Nebivolol/Valsartan Combination Tablets

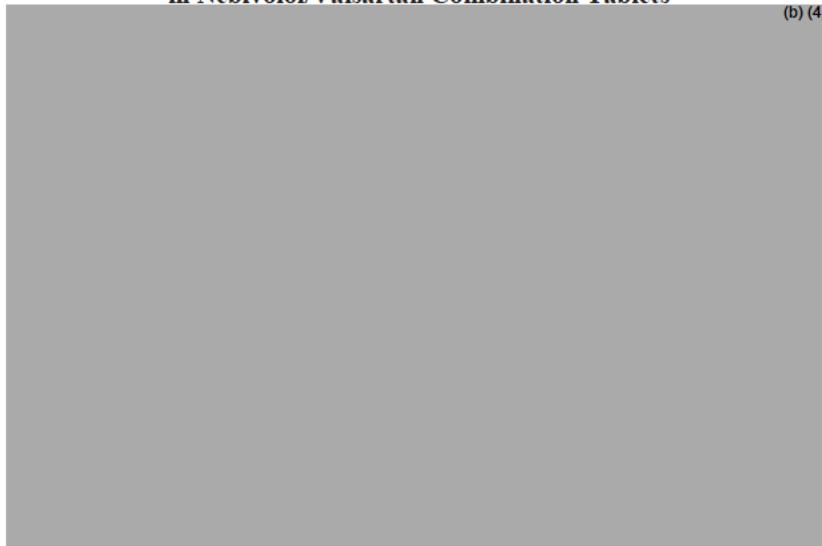
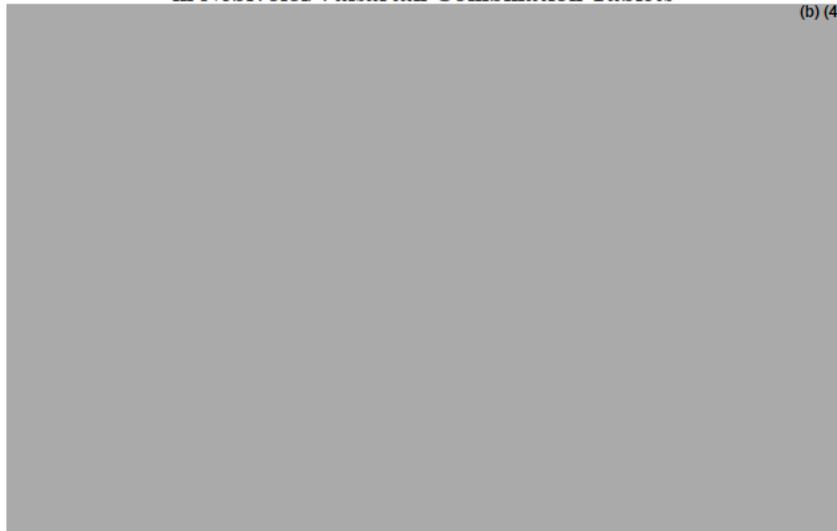


Figure 2: Comparison of USP Apparatus I (b) (4) for Valsartan Dissolution in Nebivolol/Valsartan Combination Tablets



➤ **Speed of Rotation**

The Applicant stated that a basket rotation speed of 100 rpm was selected for the fixed dose combination tablets, as rotation speeds of around 100 rpm are typical for immediate release dosage forms utilizing the USP Apparatus I.

➤ **Medium**

The Applicant provided in Table 9 the dissolution conditions used on the (b) (4) lowest strength for nebivolol/valsartan tablets in (b) (4) (b) (4) 67 mM phosphate buffer pH 6.8.

Table 9: Summary of Experiment for Regulatory Media Screening

<i>Parameter</i>	
Strength	5/80 mg (b) (4)
Apparatus	USP I (Baskets)
Speed of Rotation	100 r/min
Bath Temperature	37°C
Volume	900 mL
Sampling points	5, 15, 30, 45, and 60 minutes (w/o replacement)
Medium	(b) (4) 67 mM Phosphate buffer pH 6.8

The Applicant provided the dissolution release profiles for nebivolol and valsartan in Figure 3 and Figure 4.

Figure 3: Nebivolol Dissolution Profiles for 5/80 mg (b) (4) in (b) (4) Buffer pH 6.8 (Source: prd-rpt-anl-00595.pdf)

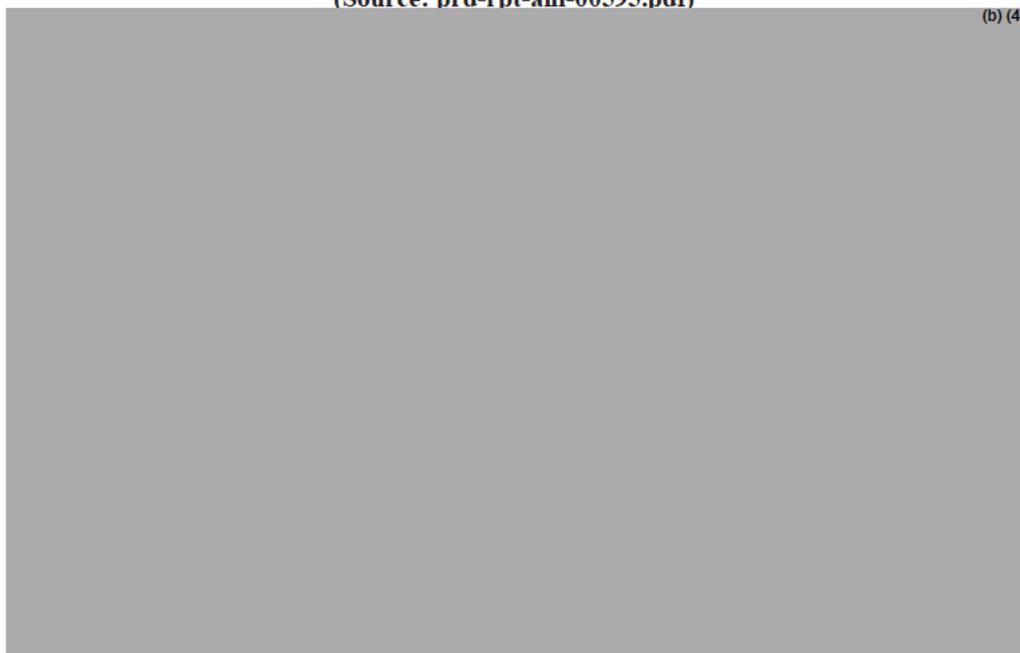


Figure 4: Valsartan Dissolution Profiles for 5/80 mg (b) (4) in (b) (4) Buffer pH 6.8

(b) (4)

The Applicant stated that nebivolol shows (b) (4)

The Applicant stated (b) (4)

The Applicant concluded (b) (4)

The Applicant provided the solubility results of nebivolol in phosphate buffer pH 6.8 in the presence of (b) (4) SDS in Table 10.

Table 10: 24-Hour Solubility of Nebivolol HCl in Phosphate Buffer pH 6.8 at 37°C in Presence of (b) (4) SDS

(b) (4)	(b) (4)
---------	---------

To achieve sink conditions (b) (4) is required. Based on the solubility results (Table 10), the Applicant determined that SDS is a much more powerful agent to enhance the solubility for nebivolol (b) (4) in pH 6.8. Therefore, SDS at a level of 0.5% was selected and the results for a dissolution run using pH 6.8 with 0.5% SDS is shown in Figure 5 and Figure 6 for nebivolol and valsartan, respectively. The dissolution conditions used to generate the figures (5 and 6) are shown in Table 11.

Table 11: Summary of Experiment for Media Screening Using Surfactant

Strength	5/80 mg (b) (4)
Apparatus	USP I (Baskets)
Speed of Rotation	100 r/min
Bath Temperature	37 °C
Volume	900 mL
Sampling points	5, 15, 30, and 45, minutes (w/o replacement)
Medium	67 mM Phosphate buffer pH 6.8 with 0.5% SDS

Figure 5: Nebivolol Dissolution Profile at pH 6.8 With and Without SDS

(b) (4)



Figure 6: Valsartan Dissolution Profile at pH 6.8 With and Without SDS

(b) (4)



Reviewer's Assessment: *SATISFACTORY*

4. What information is available to support the robustness (e.g. linearity, accuracy, etc.) of the dissolution methodology?

The Applicant used a validated method (Method PRD-TM-ANL-00985, Version 3.0) in the dissolution of nebivolol/valsartan FDC tablets. The method utilizes a gradient reverse-phase UPLC with UV detection at 290 nm to quantitate dissolution samples of Nebivolol and Valsartan. Specificity, solution stability, linearity, system precision, accuracy, repeatability, intermediate precision, and robustness were assessed and the results are provided in Table 1-1 in the following link:

<\\cdsesub1\evsprod\nda206302\0000\m3\32-body-data\32p-drug-prod\nebivolol-and-valsartan-fdc-tablet-all-strengths\32p5-contr-drug-prod\32p53-val-analyt-proc\prd-rpt-anl-00560.pdf>.

Reviewer's Assessment: *SATISFACTORY*

5. What data are available to support the discriminating power of the method?

The Applicant used the proposed dissolution test conditions (Baskets at 100 rpm, 900 mL of 67 mM phosphate buffer pH 6.8 with 0.5% SDS) (b) (4)



2 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

Reviewer's Comment:

(b) (4)

7. Is the proposed dissolution method biorelevant? What data are available to support this claim?

No, the proposed dissolution method is not biorelevant. It is intended as a quality control method.

8. Is the proposed method acceptable? If not, what are the deficiencies?

Yes, the proposed method is acceptable.

B.2. ACCEPTANCE CRITERIA

9. What are the proposed dissolution acceptance criteria for this product?

The proposed acceptance criteria are as follows:

Nebivolol: (b) (4)% (Q) at 30 minutes

Valsartan: (b) (4)% (Q) at 30 minutes

10. What data are available to support the acceptance criteria?

The Applicant stated that

(b) (4)

was required to meet the limit of NLT (b) (4)% (Q) in 30 minutes (b) (4)

The dissolution data generated on the clinical batches and the registration stability batches support an acceptance criteria of NLT $\frac{(b)}{(4)}\%$ (Q) in 30 minutes for valsartan (see Table 4-2 in section 4.0 Appendix in the following link:

<\\cdsesub1\evsprod\nda206302\0000\m2\27-clin-sum\summary-biopharm.pdf>),

and see the following link for the dissolution data of the registration stability batches:

<\\cdsesub1\evsprod\nda206302\0000\m3\32-body-data\32p-drug-prod\nebivolol-and-valsartan-fdc-tablet-all-strengths\32p8-stab\prd-rpt-anl-00562.pdf>.



The dissolution profiles of clinical trial formulations used in NAC-MD-01 for nebivolol and valsartan are shown in Figure 10 and Figure 11, respectively. Dissolution was conducted in pH 6.8 phosphate buffer with 0.5% SDS, using Type I (Basket) at 100 rpm.

Figure 10: Dissolution Profiles of Nebivolol from Nebivolol/Valsartan FDC Tablets Used in NAC-MD-01 Study (n=12) (Source: drug-product.pdf)



Figure 11: Dissolution Profiles of Valsartan from Nebivolol/Valsartan FDC Tablets Used in NAC-MD-01 Study (n=12) (Source: drug-product.pdf)



The above two figures show [redacted] (b) (4)
[redacted] % at 30 minutes.

Also, the Applicant provided

(b) (4)

[Redacted]

[Redacted]

(b) (4)

Reviewer's Comment: The Reviewer finds the proposed acceptance criterion for nebivolol of (b) (4)% (Q) at 30 minutes acceptable because of the stability data. However, the proposed acceptance criterion of (b) (4)% (Q) at 30 minutes for valsartan is not acceptable, as the clinical and stability data support (b) (4)% (Q) at 30 minutes. The Applicant is requested to revise the dissolution acceptance criterion for valsartan from (b) (4)% (Q) at 30 minutes to (b) (4)% (Q) at 30 minutes and update the specification table.

11. Is the setting of the dissolution acceptance criteria based on data from clinical and registration batches?

Yes.

12. Are mean (n=12) dissolution profile data used for the setting of the acceptance criteria?

Yes.

13. Are the acceptance criteria acceptable? If not, what are the recommended acceptance criteria?

The proposed acceptance criterion for nebivolol of (b) (4)% (Q) at 30 minutes is acceptable. However, the proposed acceptance criterion of (b) (4)% (Q) at 30 minutes for valsartan is not acceptable. The data generated on the clinical and stability data support (b) (4)% (Q) at 30 minutes for valsartan. Therefore, the Applicant is requested to revise the dissolution acceptance criterion for valsartan from (b) (4)% (Q) at 30 minutes to (b) (4)% (Q) at 30 minutes and update the specification table.

C) DRUG PRODUCT FORMULATION DEVELOPMENT and BRIDGING ACROSS PHASES

14. What is the composition of the formulation of the proposed product?

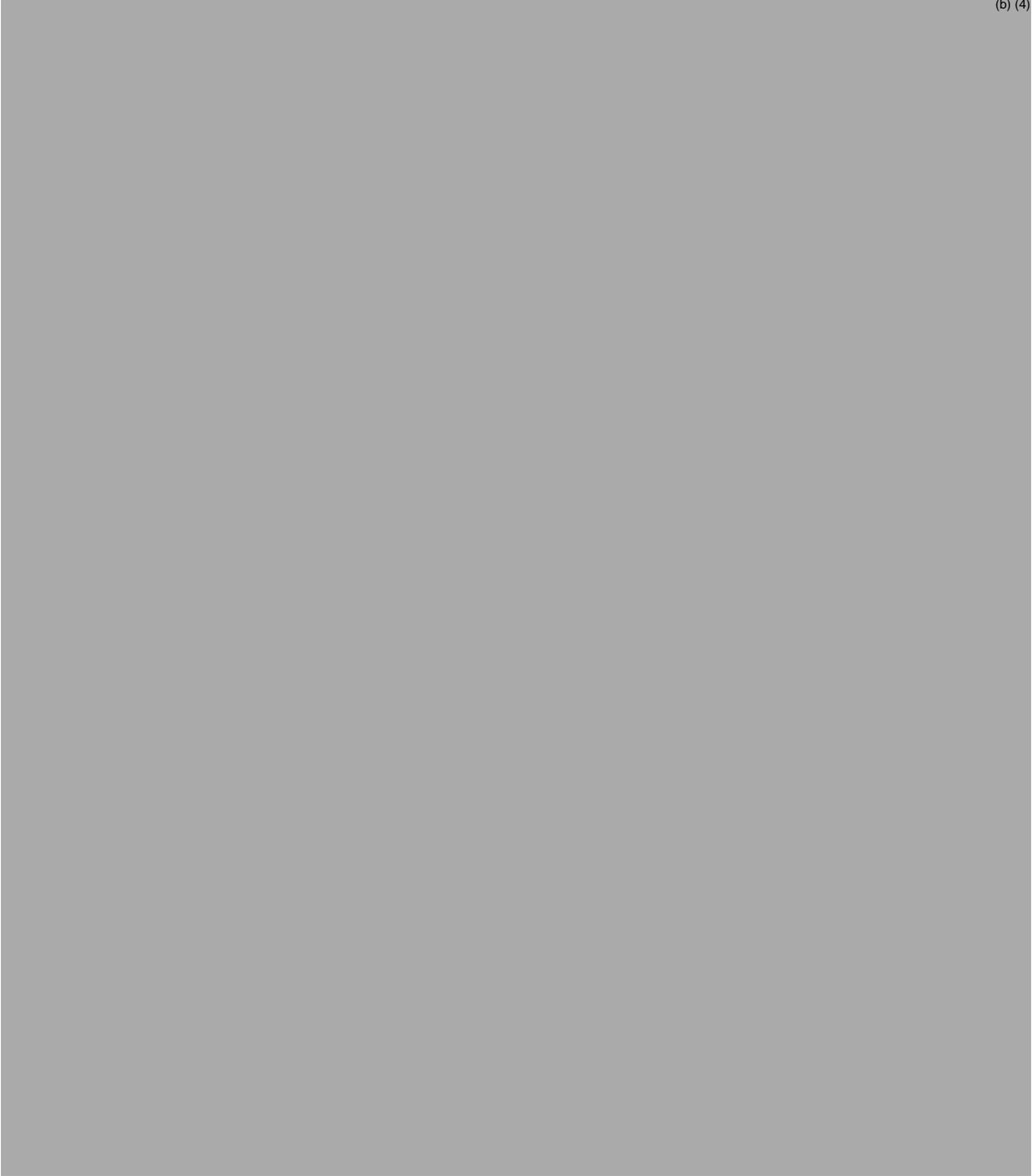
The proposed commercial product is in the form of immediate-release tablets containing a fixed-dose combination (FDC) of nebivolol and valsartan. The proposed commercial manufacturing process consists (b) (4)

[Redacted]

[Redacted] (b) (4)

D) DISSOLUTION APPLICATIONS

(b) (4)



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immediately following this page

21. Is there any IVIVR or IVIVC information submitted? What is the regulatory application of the IVIVR/IVIVC in the submission? What data are provided to support the acceptability of the IVIVR or IVIVC model?

NA

D.2 SURROGATES IN LIEU OF DISSOLUTION

22. Are there any manufacturing parameters (e.g. disintegration, drug substance particle size, etc.) being proposed as surrogates in lieu of dissolution testing? What data are available to support the approval of the proposed surrogate test?

NA

D.3 DISSOLUTION AND QBD

23. Does the application contain QbD elements? If yes, is dissolution identified as a CQA for defining design space?

Yes, the application contains QbD elements. However, dissolution is not identified as a CQA for defining design space.

24. Was dissolution included in the DoE? What raw materials and process variables are identified as having an impact on dissolution? What is the risk assessment performed to evaluate the criticality of dissolution?

The Applicant evaluated the critical attributes of the drug substances such as, particle size (valsartan), solubility (nebivolol and valsartan), stability/impurities (nebivolol and valsartan), hygroscopicity (valsartan), and solid state form (valsartan). However, the drug product attribute, dissolution, was found to have low impact on these attributes, as these attributes were studied and controlled to confirm low impact/risk.

25. What biopharmaceutics information is available to support the clinical relevance of the proposed design space?

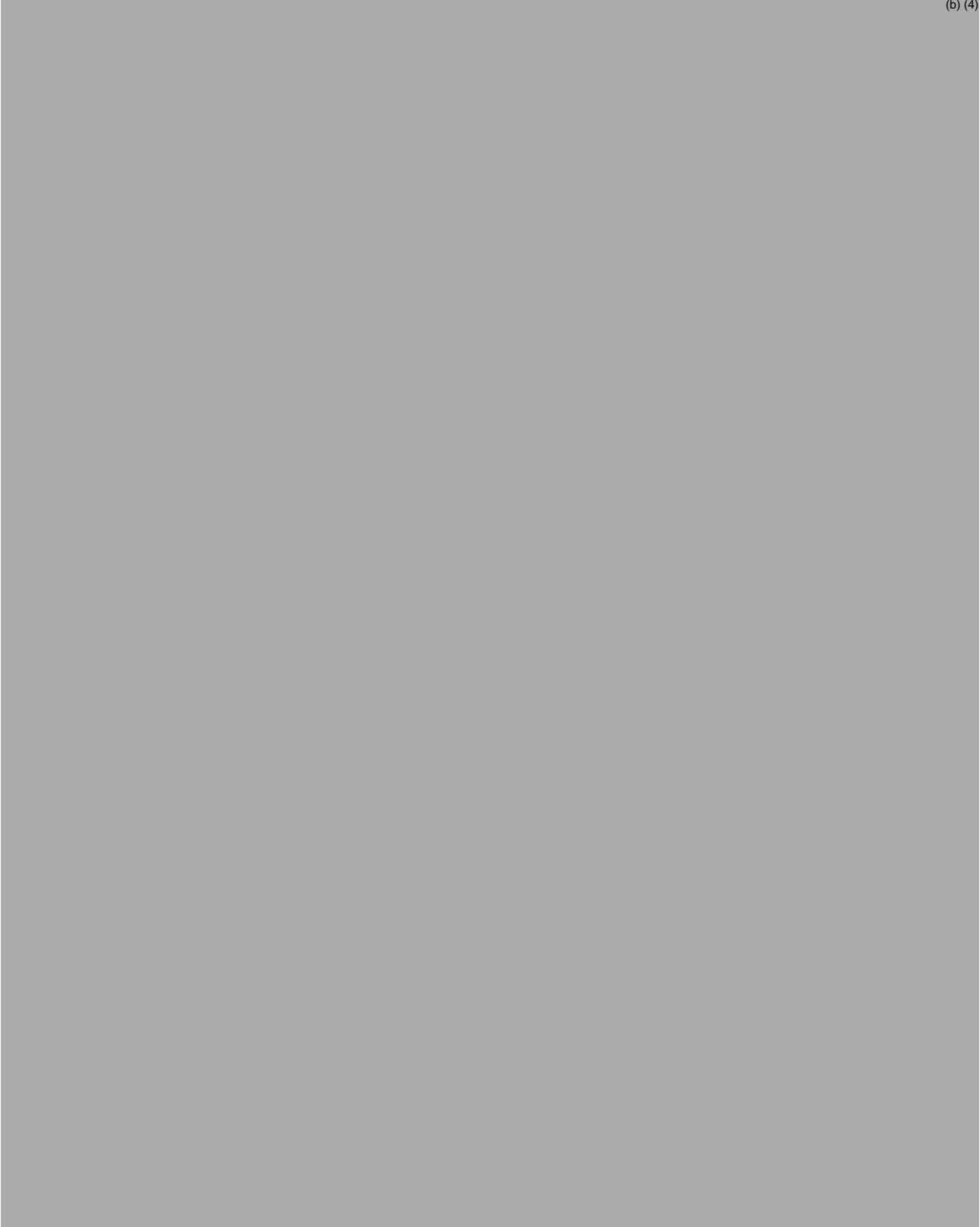
NA

26. Is there any dissolution model information submitted as part of QbD implementation? What is the regulatory application of the dissolution model in the submission? What data are provided to support the acceptability of the dissolution model?

NA

E) BIOEQUIVALENCE STUDIES

(b) (4)



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PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

NDA Number	206-302
Submission Date	February 24,2014
Product name, generic name of the active	Nebivolol/Valsartan Fixed Dose Combination
Dosage form and strength	Tablet (5/80, 5/160, 10/160, 10/320, and 20/320 mg)
Indication	For the treatment of hypertension as add-on therapy, replacement therapy, and initial therapy
Applicant	Forest Research Institute, Inc.
Clinical Division	DCRP
Type of Submission	505 (b) (2)
Biopharmaceutics Reviewer	Houda Mahayni, Ph.D.
Biopharmaceutics Team Leader	Angelica Dorantes, Ph.D.

I. SUBMISSION OVERVIEW

The Applicant developed Nebivolol (a β -adrenergic receptor blocker), and valsartan (an angiotensin II type 1 receptor blocker) Fixed Dose Combination (FDC) tablets for the treatment of hypertension as add-on therapy, replacement therapy, and initial therapy. The clinical development of this FDC was conducted under IND 109771.

The Applicant submitted NDA 206302 for Nebivolol/Valsartan FDC tablets in five strengths (5/80 mg, 5/160 mg, 10/160 mg, 10/320 mg, and 20/320 mg), pursuant to Section 505(b) (2) of the Federal Food, Drug, and Cosmetics Act. The Applicant is relying on FDA's previous findings of safety and effectiveness for the listed drug Diovan (valsartan) (NDA 20-665) for 80 and 160 mg oral capsules, and (NDA 21-283) for 80, 160, and 320 mg oral tablets. Both NDAs were submitted by Novartis Pharmaceuticals Corporation. Also, the Applicant referenced the listed drug Bystolic (nebivolol hydrochloride) (NDA 21-742) which was submitted by the Applicant (Forest Research Institute, Inc.).

The nebivolol/valsartan FDC development program consisted of six (Phase 1) studies in healthy subjects and two (Phase 3) studies in patients with stage (1 or 2) essential hypertension. The six Phase 1 studies are the following:

- **Study NAC-PK-01** to evaluate the PK interaction between nebivolol and valsartan and to determine the safety and tolerability of concomitantly administered single doses of nebivolol and valsartan in healthy subjects.
- **Study NAC-PK-03** to evaluate the PK and PD interaction between nebivolol and valsartan at steady state and to determine the safety and tolerability of concomitantly administered multiple doses of nebivolol and valsartan in healthy subjects.
- **Study NAC-PK-04** to evaluate the effect of food on the oral bioavailability of a FDC of nebivolol and valsartan.
- **Study NAC-PK-05** to compare the systemic exposures following administration of a FDC tablet of nebivolol and valsartan versus the coadministration of separate nebivolol and valsartan tablets.

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

- **Study NAC-PK-06** to characterize the pharmacokinetics and assess dose proportionality of nebivolol and valsartan following once daily administration of the FDC of nebivolol and valsartan.
- **Study NAC-PK-07** to evaluate the bioequivalence of the current FDC formulation of nebivolol and valsartan and the new FDC formulation of nebivolol and valsartan.

The two Phase 3 studies are the following:

- **Study NAC-MD-01** to assess efficacy and safety of the FDC.
- **Study NAC-MD-02** to assess long-term safety/tolerability of the free-tablet combination of nebivolol and valsartan.

The five FDC of nebivolol and valsartan were administered in the pivotal efficacy trial (NAC-MD-01): 5/80 mg, 5/160 mg, 10/160 mg, 10/320 mg and 20/320 mg. According to the Applicant the bioequivalence (BE) of nebivolol and valsartan were demonstrated between the highest strength, FDC of nebivolol/valsartan (20/320 mg) and the co-administered free combination (20 mg nebivolol + 320 mg valsartan) in Study NAC-PK-05. (b) (4)

(b) (4)

(b) (4)

II. BIOPHARMACEUTICS SUMMARY INFORMATION

According to the Applicant, Nebivolol and valsartan belong to Biopharmaceutics Classification System (BCS) Class II and IV, respectively. Both drug substances (nebivolol and valsartan) exhibit pH-dependent solubility profiles. Nebivolol is a basic drug. The pKa of the amino group in nebivolol hydrochloride is 8.4. Therefore, it exhibits low solubility at pH 6 and above, and exhibits higher solubility at low pH conditions. On the other hand, valsartan is an acidic drug, which exhibits low solubility at low pH and high solubility at high pH (≥ 5).

Drug Product:

The nebivolol/valsartan FDC tablet is intended for oral administration and contains the following excipients: lactose monohydrate, microcrystalline cellulose, copovidone, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate (b) (4) talc, ferric oxide, hypromellose, polysorbate 80, and Opadry® II film coatings. (b) (4)

(b) (4)

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

Dissolution:

(b) (4)



Review:

The Biopharmaceutics review will be focused on the evaluation and acceptability of;

- The BE study No. NAC-PK-07,
-  (b) (4)
- The dissolution method and acceptance criteria

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

III. POTENTIAL REVIEW ISSUES – DAY 74 LETTER COMMENTS

The following parameters for the ONDQA’s Product Quality - Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS				
<u>A. INITIAL</u> OVERVIEW OF THE NDA APPLICATION FOR FILING				
	Parameter	Yes	No	Comment
1.	Does the application contain dissolution data?	x		The dissolution of nebivolol/valsartan tablets is monitored during release and stability testing. The dissolution is performed in 900 mL of Phosphate Buffer pH 6.8 with 0.5% SDS using USP Apparatus I (baskets) at 100 rpm.
2.	Is the dissolution test part of the DP specifications?	x		The proposed acceptance criteria are as follows: Nebivolol: (b) (4) % (Q) at 30 minutes Valsartan: (b) (4) % (Q) at 30 minutes
3.	Does the application contain the dissolution method development report?	x		The Applicant provided the development report (PRD-RPT-ANL-00595).
4.	Is there a validation package for the analytical method and dissolution methodology?	x		
5.	Does the application include a biowaiver request?	x		(b) (4)
6.	Does the application include an IVIVC model?		x	
7.	Is there a modified-release claim? If yes, address the following: a) Is there information submitted to support the claim in accordance with 320.25 (f)? b) Is there information on the potential for alcohol-induced dose dumping?		x	The product is an immediate release oral dosage form.
8.	Is information such as BCS classification mentioned, and supportive data provided?	x		The Applicant provided solubility and permeability studies performed on nebivolol and valsartan to determine their BCS classification.
9.	Is information on mixing the product with foods or liquids included?		x	The product will be swallowed whole.

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

10.	Is there any <i>in vivo</i> BA or BE information in the submission?	x		Biopharmceutics will review Study NAC-PK-07.
11.	Is there any design space proposed using <i>in vitro</i> dissolution/drug release as a response variable?		x	There are QbD elements in the Application. (b) (4)
12.	Is the control strategy related to <i>in vitro</i> dissolution/drug release?		x	

B. FILING CONCLUSION				
	Parameter	Yes	No	Comment
13.	IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?	x		<ul style="list-style-type: none"> The NDA is fileable from Biopharmaceutics Perspective.
14.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.			Not Applicable.
15.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		x	

{See appended electronic signature page}

Houda Mahayni, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HOUDA MAHAYNI
04/25/2014

ANGELICA DORANTES
04/25/2014

ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications

IQA and Filing Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: 206302

2. DATES AND GOALS:

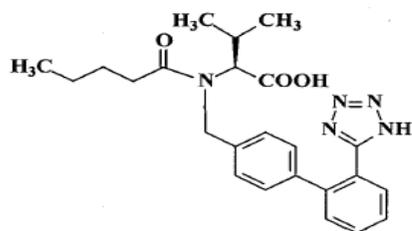
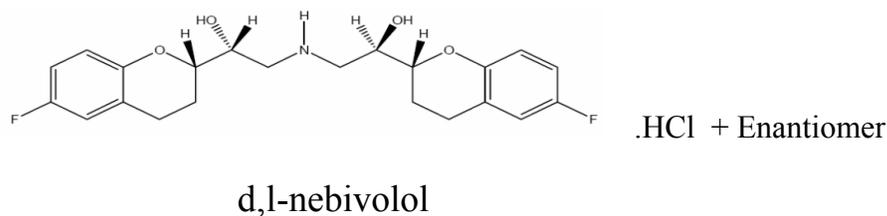
Letter Date: Feb. 21, 2014	Submission Received Date : Feb. 24, 2014
PDUFA Goal Date:	Dec. 24, 2014

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	(b) (4)
Established or Non-Proprietary Name (USAN):	Nebivolol/valsartan
Dosage Form:	Tablets, immediate release
Route of Administration	Oral
Strength/Potency	5/80, 5/160, 10/160, 10/320 and 20/320 mg
Rx/OTC Dispensed:	Rx

4. INDICATION: For the treatment of hypertension

5. DRUG SUBSTANCE STRUCTURAL FORMULA:



**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

6. NAME OF APPLICANT (as indicated on Form 356h):

Forest Laboratories, Inc.

7. SUBMISSION PROPERTIES:

Review Priority:	Standard
Submission Classification (Chemical Classification Code):	Type 4, Fixed dose combination
Application Type:	505(b)(2)
Breakthrough Therapy	No
Responsible Organization (Clinical Division):	Division of Cardiovascular and Renal Products

8. CONSULTS:

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics		X	
Clinical Pharmacology		X	
Establishment Evaluation Request (EER)	X		
Pharmacology/Toxicology		X	
Methods Validation		X	
Environmental Assessment		X	
CDRH		X	
Other	X		Microbiology

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

Overall Filing Conclusions and Recommendations

CMC:

Is the Product Quality Section of the application fileable from a CMC perspective?

Yes

Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter?

No

Biopharmaceutics:

Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective?

TBD

Biopharmaceutics Filing Issues:

See Biopharmaceutics Filing Review which will be entered separately in DARRTS

Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter?

TBD

Biopharmaceutics Comments for 74-Day Letter:

See Biopharmaceutics Filing Review which will be entered separately in DARRTS

Microbiology:

Is the Product Quality Section of the application fileable from a Microbiology perspective?

Yes

See Filing review in DARRTS by Erika Pfeiler

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

Summary of Initial Quality Assessment

Does the submission contain any of the following elements?			
Nanotechnology	QbD Elements	PET	Other, please explain
No	Yes	No	

Is a team review recommended? No
Suggested expertise for team: A single reviewer is suggested since drug substance information is in DMFs that have been previously reviewed and only the drug product information needs to be reviewed in detail.

Summary of Critical Issues and Complexities

Drug Substance:

- Amendments to DMF (b)(4) for valsartan subsequent to the last “Adequate” review dated Jan 28, 2013, should be reviewed.
- No batch analysis data are provided in the NDA; instead, reference is made to DMF (b)(4) for this information. At a minimum, shouldn’t data for valsartan batches used in the manufacture of the registration batches of product be submitted in the NDA?
- Are the proposed acceptance criteria for particle size in the valsartan specification adequately justified?
- The last review in DARRTS for DMF (b)(4) on Sep.18, 2013, covered the Amendment dated Dec.13, 2012 and deemed it to be adequate. However, a Quality Amendment submitted on Aug. 14, 2013 has not been reviewed and should be evaluated.
- Similar to valsartan, no batch analysis data have been submitted to the NDA and only a reference to the DMF for this information has been made. The need for these data for nebivolol hydrochloride batches used in the manufacture of the registration batches of product should be considered.

Drug Product

- Has the excipient compatibility study been properly executed?
- A significant amount of QbD elements has been utilized in the formulation and process development studies. These need to be critically evaluated. Particular attention should be paid to the final acceptable process ranges that have been established for each unit operation for commercial production (Table 3.2.P.2.3.13-1). Are these design spaces as defined in ICH Q8? Have they incorporated these ranges in their manufacturing procedure?
- Have batch records (master and executed) been submitted as required by regulations for a 505(b)(2) application?
- Regarding the specification –
 - The limits for assay and total impurities for the valsartan component of the fixed dose combination product are (b)(4) for

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

valsartan tablets. Is this acceptable? Has the Applicant provided any justification
[redacted] (b) (4)?

- Have the UPLC methods for assay and degradation products been adequately validated for both valsartan and nebivolol hydrochloride components? Is there a need to verify these methods at FDA's St.Louis laboratories?
- The Comparability Protocol in Section 3.2.R for demonstrating the equivalence of nebivolol hydrochloride and valsartan drug substances manufactured at alternate sites and/or manufacturers should be evaluated with input from the post-marketing division.
- [redacted] (b) (4)
- What is the reason for the proposed [redacted] (b) (4)

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

Initial Quality Assessment

This is a 505(b)(2) application for nebivolol and valsartan tablets, 5/80, 5/160, 10/160, 10/320 and 20/320 mg. Both drugs in this fixed dose combination (FDC) drug product have been previously approved under NDAs 21742 {Bystolic (nebivolol)}, 20-665 {Diovan (valsartan capsules)} and 21-283 {Diovan (valsartan tablets)}. This combination of nebivolol, a β -adrenergic receptor blocker, and valsartan, an angiotensin II type 1 receptor blocker, has been developed for the treatment of hypertension as initial, add-on or replacement therapy. Clinical development of this FDC was conducted under IND 109771. The safety and efficacy of this product were demonstrated in a multicenter, randomized, double-blind, placebo-controlled, 8 week study and one open label safety study. The Applicant claims that results from this Phase 3 efficacy study establish that the FDC produces clinically and statistically significantly greater blood pressure reduction compared to each monotherapy component.

Only one meeting with CMC issues was scheduled with the Applicant, a Pre-NDA CMC teleconference on May 21, 2013. Two questions were submitted by Forest Labs. (b) (4)

[REDACTED]

Based on these responses, Forest Labs cancelled the teleconference.

Drug Substance: Nebivolol Hydrochloride: White to almost white powder, m.p. 226-227° C, which is soluble in methanol, DMSO and DMF but sparingly soluble in ethanol, propylene glycol and polyethylene glycol. It is very slightly soluble in hexane, dichloromethane and methylbenzene. It has 4 stereogenic centers which can potentially generate 20 different stereoisomers. However, the drug substance used in this combination drug product is a racemic mixture of SRRR- nebivolol and RSSS-nebivolol. All CMC information for this synthetic drug substance is by reference to Type II DMF # (b) (4). It is also stated that information on this drug substance is (b) (4) held by the

Applicant. This DMF has been reviewed earlier and the last review dated 18 Sep. 2013 was deemed 'Adequate'. Specifications are provided in the NDA and it is claimed that a retest date of (b) (4) months is supported by the stability data submitted to the DMF.

Valsartan: is a white, fine hygroscopic powder which is (b) (4) practically insoluble in water. (b) (4)

It is manufactured by (b) (4) and DMF # (b) (4) is cross-referenced for CMC information. The LoA is (b) (4)

Specifications for valsartan are provided which generally conform to the USP monograph with additional tests for residual solvents and particle

**ONDQA Initial Quality Assessment (IQA) and Filing Review
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size. Based on the stability data in the DMF a retest date of (b) (4) months is proposed. The DMF was last reviewed on Jan 28, 2013 and found 'Adequate'.

Drug Product

The nebivolol hydrochloride, valsartan combination drug product is manufactured in 5 strengths 5/80, 5/160, 10/160, 10/320 and 20/320 mg as immediate release tablets. (b) (4)

[Redacted]

The Applicant states that a scientific and risk-based QbD approach was used in the development of this fixed dose combination product (b) (4)

[Redacted]

The manufacturing process for nebivolol/valsartan tablets consists of the following operations: (b) (4)

[Redacted]

Standard specifications for a solid oral dosage form have been proposed. Since this is a fixed dose combination product, for many of the test attributes e.g. assay, content uniformity, identification, degradation products and dissolution, two drug substances, nebivolol and valsartan are individually listed. Batch analysis data have been provided (b) (4)

[Redacted]

**ONDQA Initial Quality Assessment (IQA) and Filing Review
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The registration batches have been monitored for stability and 12 months of long term and 6 months of accelerated data are available (b) (4)

[Redacted]

Based on the data submitted and regression analysis, a shelf-life of (b) (4) months is proposed (b) (4)

[Redacted]

Additional Comments:

Categorical exclusion from Environmental Assessment has been requested based on 21CFR 25.31 (b). Facilities for inspection will be entered in the EES database shortly. Since this is not an NME, Methods Validation will not be requested at this time.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a <i>potential</i> filing issue or a <i>potential</i> review issue.				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			NA

**ONDQA Initial Quality Assessment (IQA) and Filing Review
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	Parameter	Yes	No	Comment
7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
8.	<p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		

**ONDQA Initial Quality Assessment (IQA) and Filing Review
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	Parameter	Yes	No	Comment
9.	Are additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

C. ENVIRONMENTAL ASSESMENT

	Parameter	Yes	No	Comment
11.	Has an environmental assessment or claim of categorical exclusion been provided?	X		Categorical exclusion

**ONDQA Initial Quality Assessment (IQA) and Filing Review
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D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	X		Reference to Type II DMFs (b) (4) (nebivolol HCl) and (b) (4) (valsartan)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		Reference to Type II DMFs (b) (4) (nebivolol HCl) and (b) (4) (valsartan)
14.	Does the section contain information regarding the characterization of the DS?	X		Reference to Type II DMFs (b) (4) (nebivolol HCl) and (b) (4) (valsartan)
15.	Does the section contain controls for the DS?	X		Reference to Type II DMFs (b) (4) (nebivolol HCl) and (b) (4) (valsartan)
16.	Has stability data and analysis been provided for the drug substance?	X		Reference to Type II DMFs (b) (4) (nebivolol HCl) and (b) (4) (valsartan)
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		Executed batch records provided
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any biowaivers been requested?	X		
24.	Does the section contain description of to-be-marketed container/closure system and presentations?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?	X		QbD elements employed [REDACTED] (b) (4) [REDACTED]
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	X		

**ONDQA Initial Quality Assessment (IQA) and Filing Review
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G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product			NA

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		See table below

DMF # (b) (4)	TYPE	HOLDER	ITEM REFERENCED (b) (4)	LOA DATE	COMMENTS
	IV			8-13-2013	
	IV			7-10-2012	
	III			9-2-2011	
	III			1-18-2011	
	III			8-31-2011	
	III			1-24-2011	
	III			9-2-2011	
	III			4-2-2008	
	III			10-18-2013	
	III			5-14-2012	
	III			8-19 -2013	

**ONDQA Initial Quality Assessment (IQA) and Filing Review
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			Foil: 25 micron oPA film/45 micron Al foil/60 micron PVC film		
(b) (4)	III	(b) (4)		(b) (4)	1-19-2011
	III			8-31-2011	
	II			3-21-2013	
	III			9-11-2013	
	III			1-22-2011	
	II			3-22-2013	

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

This document will be sequentially signed in DARRTS by all of the following who authored or reviewed this assessment:

See appended electronic signature page!

Kasturi Srinivasachar, Ph.D

CMC Lead

Division I, Branch 1

Office of New Drug Quality Assessment

{See appended electronic signature page!}

Olen Stephens, Ph.D.

Acting Branch Chief

Division I, Branch 1

Office of New Drug Quality Assessment

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KASTURI SRINIVASACHAR
03/21/2014

OLEN M STEPHENS
03/21/2014