CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206302Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 10/31/2016
See OMB Statement on Page 3.

NDA NUMBER
206302

NAME OF APPLICANT/NDA HOLDER
Forest Laboratories, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
N/A

ACTIVE INGREDIENT(S)	STRENGTH(S)
Nebivolol and valsartan	5/80 mg, 5/160 mg, 10/160 mg, 10/320 mg, and 20/320 mg of nebivolol/valsartan.

DOSAGE FORM
Tablet

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
U.S. Patent 7,803,838	September 28, 2010	August 29, 2026

d. Name of Patent Owner		
Forest Laboratories, Inc. Attn: Charles S. Ryan, J.D., Ph.D.	Address *(of Patent Owner)* 909 Third Avenue	
	City/State New York, NY	
	ZIP Code 10022	FAX Number *(if available)* 212-750-9152
	Telephone Number 212-224-6633	E-Mail Address *(if available)* charles.ryan@frx.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)		
	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

PSC Publishing Services (301) 443-6740 EF

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
4.2 Patent Claim Number(s) *(as listed in the patent)* — Does (Do) the patent claim(s) referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. — Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)*		

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	1/23/14

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Charles S. Ryan, J.D., Ph.D.	
Address 909 Third Avenue	City/State New York, NY
ZIP Code 10022	Telephone Number 212-224-6633
FAX Number *(if available)* 212-750-9152	E-Mail Address *(if available)* charles.ryan@frx.com

This section applies only to requirements of the Paperwork Reduction Act of 1995.

DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.

The burden time for this collection of information is estimated to average 20 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

Department of Health and Human Services
Food and Drug Administration

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N/A

ACTIVE INGREDIENT(S)	STRENGTH(S)
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For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
U.S. Patent 7,838,552	November 23, 2010	October 4, 2027

d. Name of Patent Owner	Address *(of Patent Owner)*	
Forest Laboratories, Inc. Attn: Charles S. Ryan, J.D., Ph.D.	909 Third Avenue	
	City/State New York, NY	
	ZIP Code 10022	FAX Number *(if available)* 212-750-9152
	Telephone Number	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

PSC Publishing Services (301) 443-6740 EF

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No

4.2 Patent Claim Number(s) *(as listed in the patent)* claims 1-2, 4, 7, 9 and 11	Does (Do) the patent claim(s) referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)* Treatment of hypertension. See proposed labeling at the "Indications and Usage" section.		

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
Chuck Ryan	1/23/14

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Charles S. Ryan, J.D., Ph.D.	
Address 909 Third Avenue	City/State New York, NY
ZIP Code 10022	Telephone Number 212-224-6633
FAX Number *(if available)* 212-750-9152	E-Mail Address *(if available)* charles.ryan@frx.com

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Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

Statement Under 21 U.S.C. §355(b)(2)(B) and 21 C.F.R. §314.50(i)(1)(iii)(A)

In accordance with the Federal Food Drug and Cosmetic Act (FDCA), the following statement is hereby provided for Forest Laboratories, Inc.'s Section 505(b)(2) New Drug Application relating to a nebivolol and valsartan fixed dose combination.

Under 21 U.S.C. §355(b)(2)(B) and 21 C.F.R. §314.50(i)(1)(iii)(A), we, Forest Laboratories, Inc., hereby certify that in our opinion and to the best of our knowledge, the following U.S. method of use patent does not claim a use for which Forest Laboratories, Inc. seeks approval.

Patent Number	Listed Expiry Date	Expiry of Pediatric Exclusivity (if any)
5,972,990	October 26, 2016	April 26, 2017

No statement or notice under 21 U.S.C. §355(b)(3) and 21 C.F.R. §314.52 is required with respect to this patent.

Signature: _____ Date: June 18, 2014

Name and Title: Charles S. Ryan, J.D., Ph.D., Senior Vice President, Chief IP Counsel

Paragraph II Certification Statement Under 21 U.S.C. §355(b)(2)(A)(ii) and 21 C.F.R. §314.50(i)(1)(i)(A)(2)

In accordance with the Federal Food Drug and Cosmetic Act (FDCA), the following Patent Certification is hereby provided for our Section 505(b)(2) New Drug Application relating to a nebivolol and valsartan fixed dose combination.

Under 21 U.S.C. §355(b)(2)(A)(ii) and 21 C.F.R. §314.50(i)(1)(i)(A)(2), we, Forest Laboratories, Inc., certify that in our opinion and to the best of our knowledge, the following U.S. patent is expired:

U.S. Patent No.: 5,399,578, which expired on September 21, 2012.

No statement or notice under 21 U.S.C. §355(b)(3) and 21 C.F.R. §314.52 is required with respect to this patent.

Signature: _____ Date: June 18, 2014

Name and Title: Charles S. Ryan, J.D., Ph.D., Senior Vice President, Chief IP Counsel

Amended Paragraph IV Certification Statement Under 21 U.S.C. §355(b)(2)(A) and §355(B)(3)

In accordance with the Federal Food Drug and Cosmetic Act (FDCA), the following amended Patent Certification is hereby provided for our Section 505(b)(2) New Drug Application relating to a nebivolol and valsartan fixed dose combination.

We, Forest Laboratories, Inc., hereby certify that in our opinion and to the best of our knowledge, the following U.S. patent is invalid, unenforceable, and/or will not be infringed by the manufacture, use, or sale of our nebivolol and valsartan fixed dose combination.

Patent Number	Listed Expiry Date	Expiry of Pediatric Exclusivity (if any)
6,294,197	June 18, 2017	December 18, 2017

With respect to U.S. Patent No. 5,972,990, Forest Laboratories, Inc. hereby revokes its prior Paragraph IV Certification Statement under 21 U.S.C. §355(b)(2)(A) and §355(B)(3). Instead, Forest Laboratories, Inc., hereby contemporaneously submits a statement under 21 U.S.C. §355(b)(2)(B) that, in our opinion and to the best of our knowledge, the '990 patent is a method of use patent that does not claim a use for which Forest Laboratories, Inc. seeks approval.

Statement Concerning Notice of Patent Certification to Patent Owner and NDA Holder(s) Under §355(b)(2)(A) and §355(B)(3)

As required by 21 U.S.C. §355(b)(3) of the FDCA and 21 C.F.R. §314.50, we hereby state that upon receipt from the FDA of an acknowledgement letter that this NDA is sufficiently complete to permit a substantive review, the undersigned will give (or cause to give) notice required by Section 355(b)(3) of the FDCA and 21 C.F.R. §314.52(a) to Novartis Pharmaceuticals Corporation as both the holder of NDA No. 02-1283 (for Diovan®) and as the currently-identified patent owner of the '197 patent.

This notice to the NDA holder and patent holder, which will be sent by certified mail, return receipt requested, or by FedEx courier, shall meet the requirements of 21 C.F.R. §§314.50(h), (i), 314.52(a) and (c).

As required by 21 C.F.R. §314.52(e), Forest Laboratories, Inc. will amend its NDA to include a certification that the required notice has been sent to each identified person

above and that the notice met the content requirements of 21 U.S.C. §355(b)(3)(D) and 21 C.F.R. §314.52.

Signature: _____ Date: June 18, 2014

Name and Title: Charles S. Ryan, J.D., Ph.D., Senior Vice President, Chief IP Counsel

EXCLUSIVITY SUMMARY

NDA # 206302 SUPPL # N/A HFD # 110

Trade Name: Byvalson

Generic Name: nebivolol/valsartan

Applicant Name: Forest Laboratories

Approval Date, If Known:

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

c) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (c) is "yes," how many years of exclusivity did the applicant request?
3 years

d) Has pediatric exclusivity been granted for these Active Moieties?
YES ☒ NO ☐
(valsartan)

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request? YES ☒ NO ☐

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?
YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).
N/A

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing <u>any</u> <u>one</u> of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20665	Diovan (valsartan)
NDA# 21283	Diovan (valsartan)
NDA# 21742	Bystolic (nebivolol)

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical

trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

N/A

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

1. Study NAC-MD-01: a multicenter, randomized, double-blind, placebo-controlled, 8-week study to evaluate the safety and efficacy of nebivolol and valsartan given as a fixed-

dose combination in patients with stage 1 or stage essential hypertension.

2. Study NAC-MD-02: a multicenter, open-label, single-arm, free-tablet combination, long-term study to evaluate the safety of nebivolol in combination with valsartan in patients with stage 1 or stage 2 essential hypertension.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

YES ☐ NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

N/A

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

YES ☐ NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

N/A

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

1. Study NAC-MD-01: a multicenter, randomized, double-blind, placebo-controlled, 8-week study to evaluate the safety and efficacy of nebivolol and valsartan given as a fixed-dose combination in patients with stage 1 or stage 2 essential hypertension.

2. Study NAC-MD-02: a multicenter, open-label, single-arm, free-tablet combination, long-term study to evaluate the safety of nebivolol in combination with valsartan in patients with stage 1 or stage 2 essential hypertension.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Study NAC-MD-01
IND # 109771 YES ☒ NO ☐

Study NAC-MD-02
IND # 109771 YES ☒ NO ☐

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

N/A

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

N/A

==========

Name of person completing form: Bridget Kane, MS
Title: Regulatory Project Manager
Date: 23 May 2016

Name of Office/Division Director signing form: Norman Stockbridge, MD, PhD
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

BRIDGET E KANE
05/31/2016

NORMAN L STOCKBRIDGE
05/31/2016

DEBARMENT CERTIFICATION

Forest Laboratories, Inc. hereby certifies that it did not and will not use in any capacity the service of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

Philip Hornick, MD, PhD
Vice President, Clinical Development and Medical Affairs.
Therapeutic Area Head, Cardiovascular and Metabolics
Global Medicines Development
Forest Research Institute
A Subsidiary of Forest Laboratories, Inc.

1:7:2014
Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 206302	NDA Supplement # N/A	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Byvalson Established/Proper Name: nebivolol/valsartan Dosage Form: tablet		Applicant: Forest Laboratories, LLC Agent for Applicant (if applicable):
RPM: Bridget Kane		Division: DCRP

NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☒ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check: 31 May 2016

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is 29 June 2016.	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ CR – 24 December 2015
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☒ N/A
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Reference ID: 3942080

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: CST SharePoint)

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	☒ Included
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	Letters:22Dec15; 22Aug14; 26Mar14 Reviews:23Mar16; 21Dec15; 12Aug14; 20Mar14
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☒ 2Jun16 DMEPA: ☒ 23Mar16; 22Feb16; 19Jan16; 22Oct14 DMPP/PLT (DRISK): ☒ None OPDP: ☒ 23Mar16 SEALD: ☒ None CSS: ☒ None Product Quality ☒ None Other: ☒ Patient Labeling – 23Mar2016 DPMH – 16Mar2016
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	9May14 ☒ 30Apr16 (Class 2 Resubmission); 12Nov14 (Cycle 1)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 17 Dec 2014 If PeRC review not necessary, explain: N/A	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)*	Included
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	Included
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ No mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☒ 6/30/15 (resubmission); 5Sep13
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	☒ CMC 21May13

❖ Advisory Committee Meeting(s)	☒
• Date(s) of Meeting(s)	9 September 2014
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☒ 24May16 (Division/CDTL Joint Memo); 23Dec14
Cross-Discipline Team Leader Review *(indicate date for each review)*	☒ 24May16 (Division/CDTL Joint Memo); 17Dec14
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	5Apr15 (Joint Clinical/Statistical Review); 5Dec14; 7Aug14
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	7Aug14 – clinical review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5]	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	N/A ☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☒ 5Sep14
Clinical Microbiology ☐ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☒ 28May14
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Review(s) *(indicate date for each review)*	☒ 5Apr15 (Joint Clinical/Statistical Review); 18Sep14; 1Aug14

[5] For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review; see also CDTL memo
Clinical Pharmacology review(s) *(indicate date for each review)*	☒ 29Mar16 (resubmission); 15Aug14
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ 22Oct14
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☒ 21Mar14
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews[6]	
• Tertiary review (*indicate date for each review*)	☒ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☒ Co-signatory, primary review 3May16
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	☒ 3May16 (resubmission/Quality); 24Oct14 (Quality); Biopharm (14Dec14; 24Oct14; Micro (28May14)
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	3May16 (resubmission/Quality); 24Oct14
☐ Review & FONSI *(indicate date of review)*	N/A
☒ Review & Environmental Impact Statement *(indicate date of each review)*	3May16 (resubmission/Quality); 24Oct14
❖ Facilities Review/Inspection	
☐ Facilities inspections (*action must be taken prior to the re-evaluation date*) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable 1May16; 28 Jan 16; 21Jul14; 15Apr14 Re-evaluation date: 31May2016 ☐ Withhold recommendation ☐ Not applicable

[6] Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☒ No changes ☒ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☒ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ N/A *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ N/A
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ N/A per Division Director
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

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/s/

BRIDGET E KANE
06/06/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206302

REVIEW EXTENSION – MAJOR AMENDMENT

Forest Laboratories, LLC
Attention: Betsy Kurian, PharmD
Manager, Regulatory Affairs
Harborside Financial Center
Plaza V, Suite 1900
Jersey City, NJ 07311

Dear Dr. Kurian:

Please refer to your New Drug Application (NDA) dated February 24, 2014, and resubmitted September 29, 2015 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Byvalson (nebivolol/valsartan) (b) (4) tablets.

On March 11, 2016 we received your March 11, 2016 amendment, containing the Chemistry, Manufacturing, and Controls (CMC) information as well as revised package labeling to support the 5/80mg dosage of nebivolol/valsartan FDC, a major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is June 29, 2016.

If you have any questions, please call Bridget Kane, Regulatory Project Manager, at (240) 402-2170.

Sincerely,

{See appended electronic signature page}

Edward Fromm, RPh, RAC
Chief Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

EDWARD J FROMM
03/17/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206302

INFORMATION REQUEST

Forest Laboratories, LLC
Attention: Betsy Kurian, PharmD
Manager, Regulatory Affairs
Harborside Financial Center
Plaza V, Suite 1900
Jersey City, NJ 07311

Dear Dr. Kurian:

Please refer to your New Drug Application (NDA) dated February 24, 2014, and resubmitted September 29, 2015 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Byvalson (nebivolol/valsartan) (b) (4) tablets.

We also refer to your February 12, 2016 submission containing revised draft carton and container labels in response to our Information Request dated January 29, 2016.

We have reviewed the reference material and have the following recommendations:

A. General Comments

1. Please consider removing the word "tablets" from the strength statement inside the green highlight so that the strength statement reads (b) (4) The word "tablets" after the strength statement appears redundant as it is already presented on the line above the strength statement.

B. Carton Labeling

1. As a courtesy, we want to bring the following inconsistency that appears to be a typo to your attention. We note the labeler code (first segment of NDC number) on the revised sleeve labeling is (b) (4) whereas it's "61874" on all other container labels and carton labeling.

We request that you resubmit revised carton and container draft labeling that address the above issues by *March 7, 2016*.

If you have any questions, please contact Bridget Kane, Regulatory Project Manager, at (240) 402-2170.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Division Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

NORMAN L STOCKBRIDGE
02/22/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206302

INFORMATION REQUEST

Forest Laboratories, LLC
Attention: Betsy Kurian, PharmD
Manager, Regulatory Affairs
Harborside Financial Center
Plaza V, Suite 1900
Jersey City, NJ 07311

Dear Dr. Kurian:

Please refer to your New Drug Application (NDA) dated 29 September 2015, received 29 September 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Byvalson (nebivolol/valsartan) (b) (4) tablets.

We also refer to your draft carton and container labels that were submitted as part of your NDA.

We have reviewed the reference material and have the following recommendations:

A. General Recommendations for Container Labels and Carton Labeling:

1. If only a single strength of Byvalson is going to be marketed, and the only proposed recommended dose is one tablet taken orally once daily, the usual dosage statement should read "Usual dose: Take one tablet by mouth once daily." If the proposed product has a dose range (and this is still under discussion), then the usual dosage statement would read "Usual dose: See Prescribing Information."
2. Please ensure the lot number and expiration date in the square placeholders on the container labels and carton labeling are clearly identified as such. For example, the lot number is presented as "Lot ####" with the identifier "Lot".
3. (b) (4) Please revise all container labels so they are consistent, or provide justification for the inconsistency. Please also clarify whether the proposed tablets are photosensitive or not. If not, then it appears the statement should read "Dispense in tightly closed containers."

B. Early Sample Packaging 30 Count Bottle Carton Labeling:

1. (b) (4)

C. Early Sample Packaging- Tray Labeling (for the 7 count sample bottles):

1. Please delete the NDC number from the tray labeling. Alternatively, revise the NDC numbers so that the tray and carton labeling NDC numbers are different for these two package configurations, and relocate it from the bottom of the tray labeling to the top third of the principal display panel (PDP). The last two digits of the tray labeling NDC number should be different than in the NDC number on the contained cartons because the tray holds a different number of tablets and thus is a different package size.
2. Relocate the lot number and expiration date from the bottom of the tray labeling to a side panel, so that this important information is conspicuous and viewable by the end-user when the cartons are packaged in the tray.
3. Add the net quantity to one of the side panels of the tray labeling, similar to that present on the Early Sample Packaging- Sleeve and Tray (containing 5 cartons, which contain 30 tablets each) Labeling.

D. Early Sample Packaging- Sleeve and Tray Labeling (containing 5 cartons, which contain 30 tablets each):

1. The last two digits of the sleeve and tray labeling NDC number should be different than in the NDC number present on the contained cartons. Revise the NDC numbers so that the sleeve and tray NDC number and the carton labeling NDC number are different for these two package configurations.

We request that you resubmit revised carton and container draft labeling that address the above issues by *12 February 2016*.

If you have any questions, please contact Bridget Kane, Regulatory Project Manager, at (240) 402-2170.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Division Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

NORMAN L STOCKBRIDGE
01/29/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 206302

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Forest Laboratories, LLC
Harborside Financial Center
Plaza V, Suite 1900
Jersey City, NJ 07311

ATTENTION: Betsy Kurian, PharmD
Manager, Regulatory Affairs

Dear Dr. Kurian:

Please refer to your New Drug Application (NDA) dated and received September 29, 2015, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Nebivolol/Valsartan Tablets (b) (4)

We also refer to your correspondence, dated and received September 30, 2015, requesting review of your proposed proprietary name, Byvalson.

We have completed our review of the proposed proprietary name, Byvalson and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your September 30, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact CDR Darrell Lyons, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4092. For any other information regarding this application, contact Bridget Kane, Regulatory Project Manager in the Office of New Drugs, at (240) 402-2170.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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

/s/

LUBNA A MERCHANT on behalf of TODD D BRIDGES
12/22/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206302

ACKNOWLEDGE –
CLASS 2 RESUBMISSION

Forest Laboratories, LLC
Attention: Betsy Kurian, PharmD
Manager, Regulatory Affairs
Harborside Financial Center
Plaza V, Suite 1900
Jersey City, NJ 07311

Dear Dr. Kurian:

We acknowledge receipt on 29 September 2015, of your 29 September 2015, resubmission to your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Byvalson (nebivolol/valsartan) (b) (4) tablets

We consider this a complete, class 2 response to our 24 December 2014 action letter. Therefore, the user fee goal date is 29 March 2016.

If you have any questions, please call Bridget Kane, Regulatory Project Manager, at (240) 402-2170.

Sincerely,

{See appended electronic signature page}

Edward Fromm, RPh, RAC
Chief Project Management Staff
Division of Cardiovascular & Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

EDWARD J FROMM
10/26/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206302

MEETING MINUTES

Forest Research Institute, Inc.
Attention: Kathleen Waldron, MBA
Senior Director, Regulatory Affairs
Harborside Financial Center, Plaza V
Jersey City, NJ 07311

Dear Ms. Waldron:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for nebivolol/valsartan (Byvalson) fixed-dose combination 5/80 mg, 5/160 mg, 10/160 mg, 10/320 mg, and 20/320 mg tablets.

We also refer to the meeting between representatives of your firm and the FDA on June 30, 2015. The purpose of the meeting was to discuss your proposed response to the Complete Response letter dated December 24, 2014.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please contact Sabry Soukehal, Consumer Safety Officer, at (240) 402 6187.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes and handouts

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Guidance
Meeting Date and Time:	June 30, 2015, 11:30 a.m. – 12:30 p.m. Eastern Time
Meeting Location:	White Oak, Building 22, Room 1415
Application Number:	206302
Product Name:	nebivolol/valsartan
Indication:	Treatment of hypertension as add-on, replacement, or initial therapy
Applicant Name:	Forest Research Institute, Inc.
Meeting Chair:	Norman Stockbridge, MD, PhD
Meeting Recorder:	Sabry Soukehal, RQAP-GLP

FDA ATTENDEES

*Division of Cardiovascular and Renal Products

Norman Stockbridge, MD, PhD	Director
Stephen Grant, MD	Deputy Director
Aliza Thompson, MD	Clinical Team Leader
Shen Xiao, MD, PhD	Clinical Reviewer
Michael Monteleone, MS, RAC	Associate Director for Labeling
Edward Fromm, R.Ph, RAC	Chief, Project Management Staff
Sabry Soukehal, RQAP-GLP	Consumer Safety Officer
Brian Proctor	Regulatory Health Project Manager

*Office of Clinical Pharmacology

Rajanikanth Madabushi, PhD	Clinical Pharmacology Team Leader

*Office of Biostatistics, Division of Biometrics I

Hsien Ming James Hung, PhD	Director

SPONSOR ATTENDEES

Kathleen Waldron	Senior Director, Regulatory Affairs
Betsy Kurian	Manager, Regulatory Affairs

Cornelia Haag-Molkenteller	VP, Clinical Development & TA Head Internal Medicine
David Bharucha	Senior Director, Clinical Development
William Ferguson	Associate Director, Clinical Development
Hongjie Zheng	VP, Statistical Science & Programming Biostatistics
Daniel Jia	Senior Director, Biostatistics
Shailja Dixit	Executive Director, Medical

1.0 BACKGROUND

The Applicant submitted NDA 206302 as a 505(b)(2) application for nebivolol/valsartan fixed-dose combination (FDC) for the treatment of hypertension as initial, add-on, or replacement therapy. A complete response letter (CRL) was issued on December 24, 2014 which outlined a potential path to approval.

The CRL acknowledged that many physicians and clinical guidelines promote the use of lower-dose combination antihypertensive therapies and the Division of Cardiovascular and Renal Products pointed out that low-dose FDCs should demonstrate more-or-less additive effects on blood pressure and avoidance of dose-related adverse reactions of either drug.

The CRL requested that the Sponsor determine the additivity of the nebivolol/valsartan FDC by characterizing the effects of the FDC compared with the effects of the corresponding components at the same dose. These additivity results should then be compared with similar information on approved antihypertensive FDCs.

The Applicant requested a Type B meeting to discuss the proposed data package and findings that would be used to support the approval of the 5/80 mg [redacted] (b) (4) doses of the nebivolol/valsartan FDC. The Applicant believes that the proposed data package, in principle, addresses the issues described in the CRL and is sufficient to permit review of the FDC for the proposed indications. The Applicant seeks the Division's agreement on this matter.

Preliminary responses to the submitted questions were provided to the Applicant in advance of the meeting and are copied below, followed by any additional discussion that took place during the meeting.

2.0 DISCUSSION

2.1. CLINICAL

Question 1: Does the Division agree that the efficacy of nebivolol/valsartan FDC is in line with recently approved antihypertensive FDCs, as demonstrated by the additivity results and blood pressure treatment effects presented in the briefing package?

FDA Response to Question 1: In our CR letter we recommended that you "abstract from your development program with Byvalson a characterization of the effects of the combination compared with effects of the corresponding components at the same dose and compare your results with similar information on approved combination antihypertensives, to the extent such data are available to you in drug labels or the literature. Your goal would be to show that

Byvalson doses are about as additive as are other combinations one might expect to be more mechanistically independent."

To address this issue, you assessed additivity by two different methods: (1) the placebo-adjusted additivity ratio and (2) the placebo-adjusted additivity difference.

According to your submission, compared to the other FDC doses of nebivolol/valsartan, the 5/80 mg [redacted] (b) (4) demonstrated greater additivity for both SBP and DBP. For these two doses, the point estimates for the placebo-adjusted additivity ratios ranged from 81 to (b) (4)% for SBP and from 83 to (b) (4)% for DBP. The point estimates for the placebo-adjusted additivity differences for these two doses ranged from -1.8 to (b) (4) mmHg for SBP and from -1.1 to (b) (4) mmHg for DBP, also indicating subadditivity. The mean additivity values of recently approved FDCs (i.e., agents referenced in the FDA's AC briefing book or slide presentation for which placebo-adjustments were possible) are shown in the table below, taken from your briefing document.

Table 7.2–1 Additivity Results From Recently Approved FDCs

			DBP		*SBP*	
		N	*Additivity Ratio*	*Additivity Difference*	*Additivity Ratio*	*Additivity Difference*
Exforge	Val 160/Amlo 5 mg	509	82.7%	–1.6	76.6%	–3.9
	Val 160/Amlo 10 mg	831	77.7%	–2.6	80.5%	–3.6
	Val 320/Amlo 5 mg	509	80.9%	–2.2	92.6%	–1.3
	Val 320/Amlo 10 mg	830	86.6%	–1.5	85.1%	–2.7
Tekturna HCT	Alis 150/HCTZ 12.5 mg	747	95.8%	–0.2	90.4%	–1.1
	Alis 150/HCTZ 25 mg	735	128.5%	1.3	103.5%	0.4
	Alis 300/HCTZ 12.5 mg	740	103.5%	0.2	83.9%	–2.4
	Alis 300/HCTZ 25 mg	718	127.0%	1.6	91.1%	–1.3
Tekamlo	Alis 150/Amlo 5 mg	754	104.1%	0.3	107.3%	0.9
	Alis 150/Amlo 10 mg	749	97.3%	–0.3	94.2%	–1.1
	Alis 300/Amlo 5 mg	758	91.9%	–0.9	85.3%	–2.6
	Alis 300/Amlo 10 mg	761	83.4%	–2.2	71.8%	–6.4
Valturna	Alis 150/Val 160 mg	1776	88.5%	–0.7	90.9%	–1.0
	Alis 300/Val 320 mg	1776	76.6%	–2.5	76.2%	–4.0
Twynsta	Telm 40/Amlo 5 mg	453	71.5%	–4.1	77.2%	–5.7
	Telm 40/Amlo 10 mg	422	77.3%	–4.1	73.3%	–8.1
	Telm 80/Amlo 5 mg	458	80.0%	–3.0	79.4%	–5.1
	Telm 80/Amlo 10 mg	438	74.3%	–4.8	79.7%	–6.1
	Mean of Approved FDCs		**83.7%**	**–1.2**	**82.5%**	**–2.6**

Based on the information presented in your briefing package, [redacted] (b) (4) however, that we do not agree that these analyses mean that "the efficacy" of nebivolol/valsartan FDC is in line with recently approved antihypertensive FDCs.

Additional Statistical Comment on Methodology: The comparison of additivity ratio and additivity difference to other recently approved antihypertensive FDCs should be interpreted with caution. Note that both components should contribute in a meaningful way to the effect of the FDC. Additivity ratio and additivity difference may not adequately characterize the benefits of the combination product if the effect comes mostly from one drug and the combination therapy does not provide a clinically important reduction beyond that achieved with the more effective monotherapy. Hence, for each of the monotherapy components, you should also provide the ratio of the reduction in blood pressure from the monotherapy component relative to the reduction with the FDC.

Discussion during the meeting: See attached slides 1-4.The Sponsor stated that their product produces blood pressure reductions similar to those achieved with recently approved FDCs. The Sponsor also noted that their logistic regression curves showing the probability of achieving blood pressure goals by baseline blood pressure support the efficacy of the (b) (4) dose (see slide 4).

The Division asked about the distribution of baseline blood pressures in the development program, and, specifically, the number of subjects contributing information to the right side of the logistic regression curve. The Sponsor responded that the subjects had "stage 2" hypertension and had a mean baseline blood pressure of 155/100 mmHg. The Division asked whether the Sponsor had received the "Points to Consider in Generating Graphs for Initial Therapy with Combination Hypertensive Drug" document and whether they had followed the advice given in the document when generating the plots. The Sponsor confirmed that they had.

Regarding the Division's "Additional Statistical Comment on Methodology", the Sponsor stated that they would provide the ratio of the reduction in blood pressure of the monotherapy/FDC and its 95% confidence interval in their response to the Agency's CR Letter.

Question 2: Does the Division agree that the proposed package of efficacy data presented constitutes a complete response?

FDA Response to Question 2: You have not addressed the primary basis for our Complete Response. Instead, you have chosen to pursue a possible alternative approach that we suggested. We are still open to considering this alternative approach but there are some issues that should be discussed at the upcoming meeting (see our responses to questions 3 and 4).

Of note, our CR letter stated the following: "We recognize that many physicians practice and guidelines promote use of lower-dose combination antihypertensive therapy on the basis that half or more of the treatment effect is manifest at the low dose, and, where the mechanisms are sufficiently distinct, one ought to expect more-or-less additive effects on blood pressure and avoidance of dose-related adverse reactions of either drug." While your briefing package addresses the additivity of blood pressure effects, you have not addressed the avoidance of dose-related adverse reactions at the proposed doses. Your Complete Response should also address this issue.

Discussion during the meeting: The Sponsor plans to present information on dose-related adverse events known to be associated with these drug classes. The Division agreed to this approach and stressed that, at a minimum, the Sponsor would need to show that the (b) (4)

dose was not worse than its monotherapy components from a safety and tolerability perspective. The Sponsor stated that they could certainly show that the FDC is no worse than the monotherapies, and will try to show that it is better tolerated. The Division indicated that it would be willing to consider data from sources other than the registration trials as supportive evidence of improved tolerability.

Question 3: Does the Division agree that the data presented in the briefing package support the approval of [redacted] (b) (4) (5/80 mg [redacted] (b) (4) of nebivolol/valsartan FDC for the treatment of hypertension?

FDA Response to Question 3: We believe there may be a path forward for one of the proposed doses, but not both, since the difference in blood pressure reduction between the two proposed doses appears to be small (see table below showing placebo-adjusted reductions).

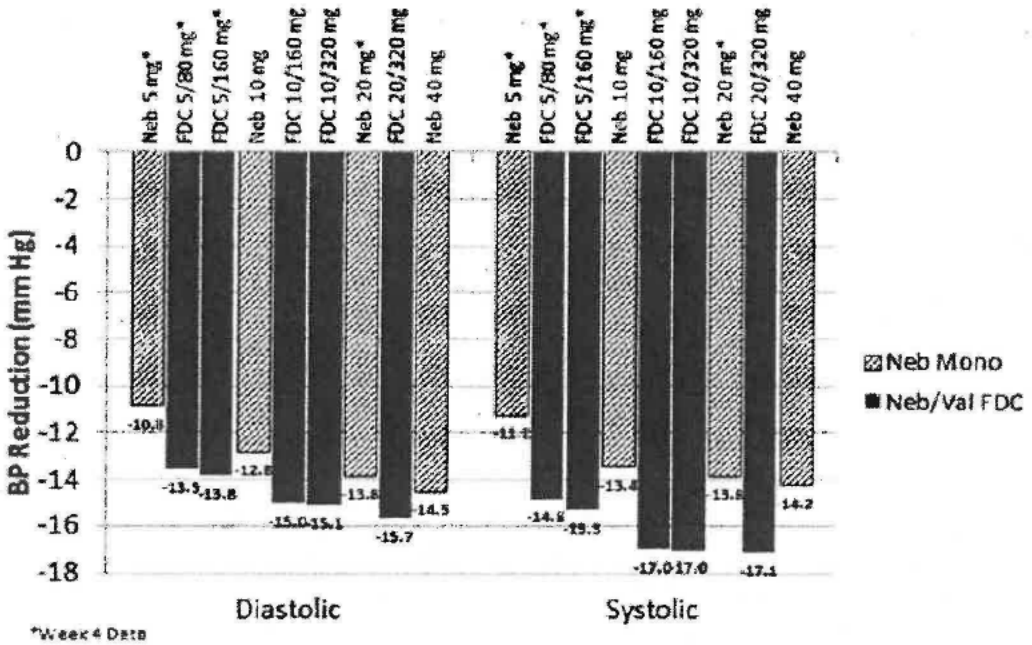
Neb/Val (mg)	Diastolic BP (mmHg)	Systolic (mmHg)
5/80 (week 4)	-7.2 (-5.9, -8.4)	-8.3 (-6.3, -10.3)
[redacted] (b) (4)		

Discussion during the meeting: The Sponsor proposed the [redacted] (b) (4) dose, with down titration to the 5/80 mg dose in patients with tolerability issues. The Division expressed skepticism that the 5/80 mg dose is better tolerated [redacted] (b) (4) The Sponsor believes there are data to support better tolerability of the 5/80 mg dose, but that the population differences are small. The Division stated that there would need to be compelling evidence of a clinically relevant difference in tolerability between the two doses to support approval of both doses.

Question 4: Does the Division agree that the benefit-risk profile of the nebivolol/valsartan FDC supports the approval of this FDC for the treatment of hypertension as add-on therapy, replacement therapy, and initial therapy?

FDA Response to Question 4: No. The available information does not support the "usual" indications for a FDC product for the treatment of hypertension (i.e., as add-on therapy, replacement therapy, and/or initial therapy). Although we are open to considering a new paradigm for approving FDC products for the treatment of hypertension, this new paradigm also means a different approach to labeling. As shown in the figure below, the proposed low dose of nebivolol/valsartan (5/80 mg) does not appear to provide an advantage in blood pressure reduction over nebivolol 20 mg or 40 mg [redacted] (b) (4)

We believe that the indication and usage statement would need to address this issue (possibly as a limitation of use). There should be further discussion of possible indications for your product at the upcoming meeting.



Source: Summary of Clinical Efficacy, NDA 206302

Discussion during the meeting: The Sponsor proposed the following indication: "for treatment of hypertension [redacted] (b) (4) ". The Division observed that based on the Sponsor's logistic regression curves, it might be possible that the indication would state that is appropriate for initial therapy. The Division then noted that the indication statement refers to beta-blockers and ARBs and not the specific beta-blocker and ARB that are components of this FDC. The Division indicated that justification would be needed to retain the proposed language. The Sponsor stated that they would give further thought to the indication statement and noted that it may include references to the standard categories (i.e., use as initial, add-on and replacement therapy).

The Division confirmed that the magnitude of the treatment differences between the FDC [redacted] (b) (4) dose and the monotherapies was sufficient to support moving forward.

2.2. REGULATORY

Question 5: Does the Division agree with the approach of using an updated Clinical Overview to fulfill the resubmission requirement?

FDA Response to Question 5: Yes.

Discussion during the meeting: This question was not discussed during the meeting.

Question 6: Does the Division agree with the organization of the electronic Common Technical Document (eCTD) as outlined in the table of contents to constitute a complete response?

FDA Response to Question 6: Yes.

Discussion during the meeting: This question was not discussed during the meeting.

3.0 OTHER IMPORTANT INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g., trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication X*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section XXX*
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items identified during the meeting.

6.0 ATTACHMENTS AND HANDOUTS

The Sponsor handed out the four-page summary below.

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/s/

NORMAN L STOCKBRIDGE
07/27/2015

PeRC PREA Subcommittee Meeting Minutes
December 17, 2014

PeRC Members Attending:
Lynne Yao
Wiley Chambers
George Greeley
Lily Mulugeta
Dianne Murphy
Greg Reaman
Hari Cheryl Sachs
Michelle Roth-Cline
Tom Smith
Suresh Pagay
Karen Davis-Bruno
Olivia Ziolkowski
Rosemary Addy
Barbara Buch
Nisha Jain Non-Responsive
Barbara Buch
Peter Starke

PREA

10:30	BLA	Non-Responsive		
10:40	NDA			
10:50	NDA			
11:00	NDA			
11:25	NDA			
	NDA			
	NDA	*206302*	*Byvalson (nebivolol/valsartan) Full Waiver*	*Treatment of hypertension*

Non-Responsive

2 Pages have been Withheld in Full as Non Responsive immediately following this page

Non-Responsive

Byvalson (nebivolol/valsartan) Full Waiver

- Proposed Indication: treatment of hypertension.
- This application triggered PREA as a new: indication, active ingredient, dosage form, dosing regimen, and route of administration.
- The sponsor has submitted an Agreed iPSP with their NDA application.
- The PDUFA goal date is December 24, 2014.
- *PeRC Recommendations*:
    - The PeRC agreed with the Division to grant a full waiver in pediatric patients because product fails to represent a meaningful therapeutic benefit over existing therapies and is unlikely to be used in substantial number of pediatric patients.

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/s/

GEORGE E GREELEY
01/05/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 206302

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Forest Laboratories, Inc
Harborside Financial Center
Plaza V, Suite 1900
Jersey City, NJ 07311

ATTENTION: Kerri Kaplan, PharmD
Senior Manager, Regulatory Affairs

Dear Dr. Kaplan:

Please refer to your New Drug Application (NDA) dated February 23, 2014, received February 24, 2014, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Nebivolol/Valsartan Tablets, 5 mg /80 mg, 5 mg/160 mg, 10 mg/160 mg, 10 mg/320 mg, and 20 mg/320 mg.

We also refer to your correspondence, submitted and received June 12, 2014, requesting review of your proposed proprietary name, Byvalson.

We have completed our review of the proposed proprietary name, Byvalson, and have concluded that it is acceptable.

If <u>any</u> of the proposed product characteristics as stated in your June 12, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Cherye Milburn, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2084. For any other information regarding this application, contact Michael Monteleone, Regulatory Project Manager in the Office of New Drugs, at (301) 796-1952.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
08/22/2014

From:	Knight Yvonne
To:	Kathleen.waldron@frx.com
Cc:	Knight Yvonne
Subject:	Information Request for NDA 206302 (Prompt Response)
Date:	Friday, August 01, 2014 3:11:03 PM
Importance:	High

Good afternoon Ms. Waldron,

We have an information request concerning Forest Lab's New Drug Application (NDA) for NDA 206302. We request a prompt response to this IR request no later than **Friday COB August 8, 2014**.

Please address the following comments and recommendations:

1. It is noted that the drug products used in the clinical trial NAC-MD-01 were [redacted] (b) (4) (FDCs and monotherapies). Therefore, submit dissolution profile data [redacted] (b) (4) used in the study using the proposed dissolution method (Baskets, 900 mL of 67 mM Phosphate buffer pH 6.8 with 0.5% SDS, 100 rpm). Provide complete dissolution profiles on n=12 units for each strength as encapsulated and non-encapsulated products (FDCs and monotherapies) using the following sampling points: 5, 10, 15, 20, 25, and 30 minutes . Calculate the similarity factor using f2 or other approaches to document profiles similarity.

2. 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 confirming this.

3. We noticed [redacted] (b) (4) at the time of lot release. To aid in the assignment of shelf-life, please provide regression analyses of the dissolution study results and total impurities content results for the drug product stability lots.

4. [redacted] (b) (4) This study will elucidate potential drug product quality risks related to the different container closure sources.

5. Provide updated real time stability study results of the NDA registration batches.

6. 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

Please confirm receipt of this Information Request. Also, please provide me with a courtesy copy via email when you submit your official amendment? Note: Official amendments need to be submitted by due date in order to be included in the review cycle. If you have any questions or comments feel free to contact me.

Best Regards,

Yvonne Knight, MS
Regulatory Health Project Manager
Division of New Drug Quality Assessment
FDA/CDER/OPS/ONDQA
10903 New Hampshire Avenue
Bldg. 21, Room 2667

Silver Spring, MD 20993-0002
Phone: 301.796.2133
Email: yvonne.knight@fda.hhs.gov

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/s/

YVONNE L KNIGHT
08/01/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206302

PROPRIETARY NAME REQUEST WITHDRAWN

Forest Laboratories, Inc
Harborside Financial Center
Plaza V, Suite 1900
Jersey City, NJ 07311

ATTENTION: Kerri Kaplan, PharmD
Senior Manager, Regulatory Affairs

Dear Dr. Kaplan:

Please refer to your New Drug Application (NDA) dated February 23, 2014, received February 24, 2014, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Nebivolol/Valsartan Tablets, 5 mg /80 mg, 5 mg/160 mg, 10 mg/160 mg, 10 mg/320 mg, and 20 mg/320 mg.

We also refer to:

- Your correspondence, dated and received February 26, 2014, requesting review of your proposed proprietary name (b) (4)
- Our letter, dated March 26, 2014, notifying you of Conditional Acceptance of the proposed proprietary name (b) (4)
- Your correspondence, dated and received on June 11, 2014, notifying us that you are withdrawing (b) (4) as the proposed proprietary name

This proprietary name is considered withdrawn as of June 11, 2014.

Finally, we refer to your correspondence, dated and received June 12, 2014, requesting review of your proposed proprietary name, Byvalson. Upon preliminary review of your submission, we have determined that it is a complete submission as described in the Guidance for Industry, Contents of a Complete Submission for the Evaluation of Proprietary Names, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf

Therefore, the user fee goal date is September 10, 2014.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Cherye Milburn, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2084. For any other information regarding this application, contact Michael Monteleone, Regulatory Project Manager in the Office of New Drugs, at (301) 796-1952.

Sincerely,

{See appended electronic signature page}

Cherye Milburn
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CHERYE D MILBURN
06/30/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206302

FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED

Forest Laboratories, Inc.
Attention: Kerri Kaplan, PharmD
Senior Manager, Regulatory Affairs
Harborside Financial Center
Plaza V, Suite 1900
Jersey City, NJ 07311

Dear Dr. Kaplan:

Please refer to your New Drug Application (NDA) dated February 21, 2014, received February 24, 2014, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for nebivolol/valsartan fixed dose combination 5/80, 5/160, 10/160, 10/320 and 20/320 mg tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is December 24, 2014.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by November 24, 2014.

We request that you submit the following information:

Microbiology:

You propose waiving microbial limits release testing for your drug product. This proposal may be acceptable provided adequate upstream controls are established and documented. More information on your process is needed. Address the following points.

1) Identify and justify critical control points in the manufacturing process that could affect microbial load of the drug product.

   a. Define the maximum processing time (b) (4)

   b. Define the maximum holding time for the coating solution.

2) Describe microbiological monitoring and acceptance criteria for the critical control points that you have identified. Conformance to the acceptance criteria established for each critical control point should be documented in the batch record in accordance with 21 CFR 211.188.

3) Verify the suitability of your microbiological testing methods for your drug product.

Clinical

4) Valsartan has little effect on diastolic blood pressure when added to a full dose of nebivolol. You need to justify why this is useful. For example, since various combination doses had similar effects, you might sustain an argument that using lower doses in combination gives at least as good a blood pressure effect but is better tolerated than is the high dose of nebivolol.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.

During our preliminary review of your submitted labeling, we have identified the following labeling issues:

Under **HIGHLIGHTS:**

1. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

   Comment: *Statement should be centered.*

2. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

   Comment: *Revise "β-blocker" to read "beta adrenergic blocker"*

In **FULL PRESCRIBING INFORMATION**:

3. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]"* or *"*[*see Warnings and Precautions (5.2)*]".

   Comment: *Check appropriate capitalization of 'see' in sections 4 and 5.*

4. In the BW, all text should be **bolded**.

   Comment: *Bold text.*

5. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

   "The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

   Comment: *Include disclaimer, modified to read, "The following adverse reactions have been identified during post-approval of either nebivolol or valsartan…."*

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by May 26, 2014 The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), and patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and patient PI, and you believe the labeling is close to the final version.
For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, please call Michael Monteleone, Regulatory Project Manager, at (301) 796-1952.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

NORMAN L STOCKBRIDGE
05/06/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 206302

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

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

ATTENTION: Kerri Kaplan, PharmD
Senior Manager, Regulatory Affairs.

Dear Dr. Kaplan:

Please refer to your New Drug Application (NDA) dated February 23, 2014, and received February 24, 2014, under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Nebivolol and Valsartan Tablets, 5 mg/80 mg, 5 mg/160 mg, 10 mg/160 mg, 10 mg/320 mg, and 20 mg/320 mg.

We also refer to your, correspondence, dated and received February 26, 2014, requesting review of your proposed proprietary name (b) (4) We have completed our review of the proposed proprietary name, (b) (4) and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your February 26, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Cherye Milburn, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2084. For any other information regarding this application, contact Michael Monteleone, Regulatory Project Manager, in the Office of New Drugs at (301) 796-1952.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
03/26/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206302

NDA ACKNOWLEDGMENT

Forest Laboratories, Inc.
Attention: Kerri Kaplan, PharmD
Senior Manager, Regulatory Affairs
Harborside Financial Center
Plaza V, Suite 1900
Jersey City, NJ 07311

Dear Dr. Kaplan:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Nebivolol / Valsartan fixed dose combination

Date of Application: February 21, 2014

Date of Receipt: February 24, 2014

Our Reference Number: NDA 206302

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 25, 2014, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, please call Michael Monteleone, Regulatory Project Manager, at (301) 796-1952.

Sincerely,

{See appended electronic signature page}

Edward Fromm, RPh, RAC
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

EDWARD J FROMM
03/06/2014

Form Approved: OMB No. 0910 - 0297 Expiration Date: December 31, 2015. See instructions for OMB Statement, below.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

PRESCRIPTION DRUG USER FEE COVERSHEET

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on FDA's website:
http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm119184.htm

1. APPLICANT'S NAME AND ADDRESS

FOREST LABORATORIES INC
Kerri Kaplan
Harborside Financial Center
Plaza V, Suite 1900
Jersey City
NJ 07311
US

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

206-302

2. NAME AND TELEPHONE NUMBER OF REPRESENTATIVE
201-427-8550

APPEARS THIS WAY ON ORIGINAL

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

[X] YES [ ] NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.
IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

[X] THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION

[ ] THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

PRODUCT NAME
bisoprolol and valsartan

6. USER FEE I.D. NUMBER
PD3013947

7. ARE YOU REDEEMING A PRIORITY REVIEW VOUCHER FOR THE TREATMENT OF TROPICAL DISEASES?
[ ] YES [X] NO

PRIORITY REVIEW VOUCHER NUMBER:

8. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.
[ ] A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)
[ ] THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food,Drug, and Cosmetic Act
[ ] THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY

9. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? [ ] YES [X] NO
If a waiver has been granted, include a copy of the official FDA notification with your submission.

Privacy Act Notice:
This notice is provided pursuant to the Privacy Act of 1974, 5 U.S.C. 552a. The collection of this information is authorized by 21 U.S.C. 371, 379, 379e, 379h, 379h-1, 379j, 379j-12, 379j-21, 387s, and 393(d)(2); 42 U.S.C. 263b(r)(1); 5 U.S.C. 301 and 552; and 42 U.S.C. 3101. FDA will use the information to assess, collect and process user fee payments, and, facilitate debt collection under the Debt Collection Improvement Act. FDA may disclose information to courts and the Department of Justice in the context of litigation and requests for legal advice; to other Federal agencies in response to subpoenas issued by such agencies; to HHS and FDA employees and contractors to perform user fee services; to the National Archives and Records Administration and General Services Administration for records management inspections; to the Department of Homeland Security and other Federal agencies and contractors in order to respond to system breaches; to banks in order to process payment made by credit card; to Dun and Bradstreet to validate submitter contact information, and to other entities as permitted under the Debt Collection Improvement Act. Furnishing the requested information is mandatory. Failure to supply the information could prevent FDA from processing user fee payments. Additional detail regarding FDA's use of information is available online: http://www.fda.gov/RegulatoryInformation/FOI/PrivacyAct/default.htm.

OMB Statement:
Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Information Management (HFA-710)
1350 Piccard Drive, 4th Floor

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB

Rockville, MD 20850	Office of Information Management (HFA- 710) 1350 Piccard Drive, 4th Floor Rockville, MD 20850 control number.

PRINTED NAME AND SIGNATURE OF AUTHORIZED REPRESENTATIVE	TITLE	DATE

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
$2,169,100.00

Form FDA 3397 (03/12)

INSTRUCTIONS FOR COMPLETING PRESCRIPTION DRUG USER FEE COVER SHEET FORM FDA 3397

Form FDA 3397 is to be completed for and submitted with each new drug or biologic product original application or supplemental application submitted to the Agency, unless specifically exempted below. Form FDA 3397 should be placed in the first volume of the application with the application (FORM FDA 356(h)) form. Form FDA 3397 is to be completed on-line at https://userfees.fda.gov/OA_HTML/pdufaCScdLogin.jsp. If you need assistance in completing the form call 301-796-7200 or email: userfees@fda.gov.

NOTE: Form FDA 3397 need not be submitted for:

CDER

505(j) applications
Supplements to 505(j) applications
351(k) applications

CBER

Any supplement that does not require clinical data for approval.
Applications and supplements for:

* Products for further manufacturing use only
* Whole blood or blood components for transfusion
* Bovine blood product for topical application licensed before September 1, 1992
* A crude allergenic extract product
* An in vitro diagnostic biological product licensed under Section 351 of the PHS Act
* 351(k) applications

ITEM NO.	INSTRUCTIONS
1-2.	**Self-explanatory**
3.	**PRODUCT NAME:** Include generic or proper name and trade name, as applicable.
4.	**BLA STN / NDA NUMBER - FOR AN ORIGINAL BIOLOGIC LICENSE APPLICATION (BLA) -** Indicate the 6-digit BLA number (Submission Tracking Number (STN)) if pre-assigned, otherwise leave blank. For A **SUPPLEMENT** enter the BLA STN. **FOR DRUG PRODUCTS:** Indicate the new drug application (NDA) number. NDA numbers can be obtained by completing the information at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm114027.htm.
5.	**CLINICAL DATA:** The definition of 'clinical data' for the assessment of user fees is found in FDA's Guidance for Industry: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees. FDA's guidance on the definition of clinical data can be found on FDA's web site: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf.
6.	**USER FEE I.D. NUMBER:** Please include the ID number (generated when completing Form FDA 3397) on the application payment check.
7.	**PRIORITY REVIEW VOUCHER:** If you are redeeming a priority review voucher awarded to a sponsor of a tropical disease product application (see section 524 of the Federal Food, Drug, and Cosmetic Act (FD&C Act)), please include the priority review voucher number assigned when the voucher was initially granted. See FDA´s Guidance for Industry: Tropical Disease Priority Review Vouchers for further information. FDA´s guidance can be found on FDA´s web site: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080599.pdf.

8.	**EXCLUSIONS:** The application is for an orphan drug product. Under section 736(a) (1) (F) of the FD&C Act, a human drug application is not subject to an application fee if the proposed product is for a rare disease or condition designated under section 526 of the FD&C Act (orphan drug designation) AND the application does not include an indication that is not so designated. A supplement is not subject to an application fee if it proposes to include a new indication for a rare disease or condition, and the drug has been designated pursuant to section 526 for a rare disease or condition with regard to the indication proposed in the supplement. A copy of the FDA letter granting orphan designation should be included with the BLA/NDA submission.
9.	**WAIVER:** Complete this section only if a waiver of user fees, including the small business waiver, has been granted for this application. *A copy of the official FDA notification that the waiver has been granted must be provided with the BLA/NDA submission.*

Form FDA 3397 (03/2012)(BACK)

Close Print Cover sheet

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 109771

MEETING PRELIMINARY COMMENTS

Forest Laboratories, Inc.
Attention: Kerri Kaplan, PharmD
Senior Manager, Regulatory Affairs
Harborside Financial Center
Plaza V, Suite 1900
Jersey City, NJ 07311

Dear Dr. Kaplan:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for nebivolol/valsartan fixed dose combination.

We also refer to your July 9, 2013, correspondence, received July 9, 2013, requesting a meeting to discuss your upcoming NDA submission.

Our responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, please call Michael Monteleone, Regulatory Project Manager, at (301) 796-1952.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: Cancelled
Meeting Location: Cancelled

Application Number: IND 109771
Product Name: nebivolol/valsartan
Indication: treatment of hypertension
Sponsor/Applicant Name: Forest Laboratories, Inc

Introduction:
This material consists of our responses to your questions and any additional comments in response to your questions. We believe that our responses adequately address your questions and so we are cancelling the meeting scheduled for September 12, 2013.

1.0 BACKGROUND

On July 9, 2013 the sponsor, Forest Laboratories, requested a meeting to discuss the proposed safety and efficacy content of a planned NDA and to obtain agreement with the Division that the pivotal and supportive studies to be included in the NDA are sufficient to permit the review of nebivolol/valsartan fixed dose combination for the treatment of hypertension.

2. DISCUSSION

Question 1: *Does the Division concur that the single positive efficacy study (NAC-MD-01) can support the NDA filing and potential approval of nebivolol/valsartan FDC for the treatment of hypertension as add-on therapy, replacement therapy, and initial therapy?*

Response: Yes.

As noted in previous discussions and correspondence, the Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry Applications Covered by Section 505(b)(2) (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had

challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

Please note that if you choose to rely on FDA's finding of safety and/or effectiveness for a listed drug(s) and you intend to use your proposed comparative clinical trial to establish a bridge between your proposed drug product and the specified listed drug(s), then you should use the specified listed drug(s) (rather than a bioequivalent ANDA product or a non-U.S. approved version of the product) as the comparator.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary

Reference ID: 3368392

name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

We note that information and questions in your background document suggest that you may intend to reference information from the SBA or FDA reviewers' public summaries for support of safety and/or effectiveness in a future NDA application. This is not acceptable. 505(b)(1) and 505(b)(2) NDAs require "full reports of investigations" of safety and effectiveness and the SBA is considered a summary.

Finally, please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

Question 2: *Does the Division agree that the data presented from NAC-MD-01 in the briefing package support the approval of all 5 dosage strengths (5/80 mg, 5/160 mg, 10/160 mg, 10/320 mg, 20/320 mg) of nebivolol/valsartan FDC?*

Response: In addition to showing a larger effect than the highest approved dose of the monotherapy components, the approved dosage strengths should be distinguishable from each other with regard to blood pressure effects and hence represent a reasonable strategy for dose titration. Based on the data you have provided, the change from baseline in blood pressure appears to be similar for some of the FDC dosage strengths (see for example Table 6.4.1.5.2.1-2 showing a similar LSM change from baseline in blood pressure in the 10/160, 10/320 and 20/320 mg strengths of nebivolol/valsartan). Given these data, the utility of all proposed dosage strengths is unclear to us, but ultimately this will be a review issue.

Question 3: *If so, does the Division agree with the Sponsor's plan to present data on all 5 dosages in the prescribing information, similar to Table 1 in Section 14 of the meeting background materials, Clinical Studies, of the Valturna PI?*

Response: Please see the answer to question 2 regarding the approval of all 5 dosage strengths.

Question 4: *Does the Division concur with Forest's proposal not to include an Integrated Summary of Safety (ISS) in the NDA?*

Response: Yes.

Reference ID: 3368392

Question 5: *Does the Division concur with the proposal not to include an Integrated Summary of Efficacy (ISE) for the NDA?*

Response: Yes.

Question 6: *Does the Division agree with the approach of using the Summary of Clinical Safety and the Summary of Clinical Efficacy to fulfill the requirements of the ISS and ISE?*

Response: Yes.

Question 7: *Does the Division concur that the estimated exposure data in hypertension patients are adequate to support the NDA?*

Response: Yes.

Question 8: *Does the Division concur with the submission of case report forms and narratives only for subjects who discontinued due to an adverse event (AE) or experienced a serious adverse event (SAE), including death?*

Response: Yes.

Question 9: *Does the Division agree that the clinical pharmacology package is adequate to support the registration of nebivolol/valsartan FDC for the treatment of hypertension?*

Response: For the most part, the clinical pharmacology package appears to be adequate to support the NDA. However, it is not clear to us how you are proposing to establish bioequivalence for all proposed strengths.

Question 10: *Does the Division agree with the Sponsor's decision to only include Module 4.3, Literature References, and to utilize Module 2.4 to reference original NDAs?*

Response: Yes.

Question 11: *Does the Division agree with the organization of the eCTD as outlined in the Table of Contents?*

Response: Yes.

Question 12: *Does the Division agree with Forest's plan for submitting study-level data sets in the NDA?*

Response: Yes. Please also see attached request for site-level data from the Office of Scientific Investigations.

Question 13: *Does the Agency agree to a full waiver for pediatric studies?*

Reference ID: 3368392

Response: Requests for a deferral/waiver of pediatric studies are reviewed by the Pediatric Review Committee. Pediatric studies of fixed-dose combination products for the treatment of hypertension are not typically required and the Division will likely support a request for a waiver. See also discussion below on PREA Requirements.

Additional Comments:
The submission should contain information on the 24-hour blood pressure lowering effects of the fixed-dose combinations and monotherapies. As an example, see Figure 3 of the prescribing information for Edarbyclor (azilsartan medoxomil and chlorthalidone).

3.0 OTHER IMPORTANT INFORMATION

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the following labeling review resources: the Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products, labeling guidances, and a sample tool illustrating the format for Highlights and Contents (Table of Contents) available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting held on or after November 6, 2012. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Pediatric and Maternal Health Staff at 301-

Reference ID: 3368392

796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

Reference ID: 3368392

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct the inspections (Item I and II).

The dataset that is requested as per Item III below, is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 2, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and specific Clinical Investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed Phase 3 clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Current Location of Principal Investigator (if no longer at Site): Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)

2. Please include the following information in a tabular format by site in the original NDA for each of the completed Phase 3 clinical trials:
   a. Number of subjects screened for each site by site
   b. Number of subjects randomized for each site by site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed Phase 3 clinical trials:
   a. Location of Trial Master File [actual physical site(s) where documents are maintained and would be available for inspection]
   b. Name, address and contact information of all CROs used in the conduct of the clinical trials
   c. The location (actual physical site where documents are maintained and would be available for inspection) for all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies
   d. The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.)

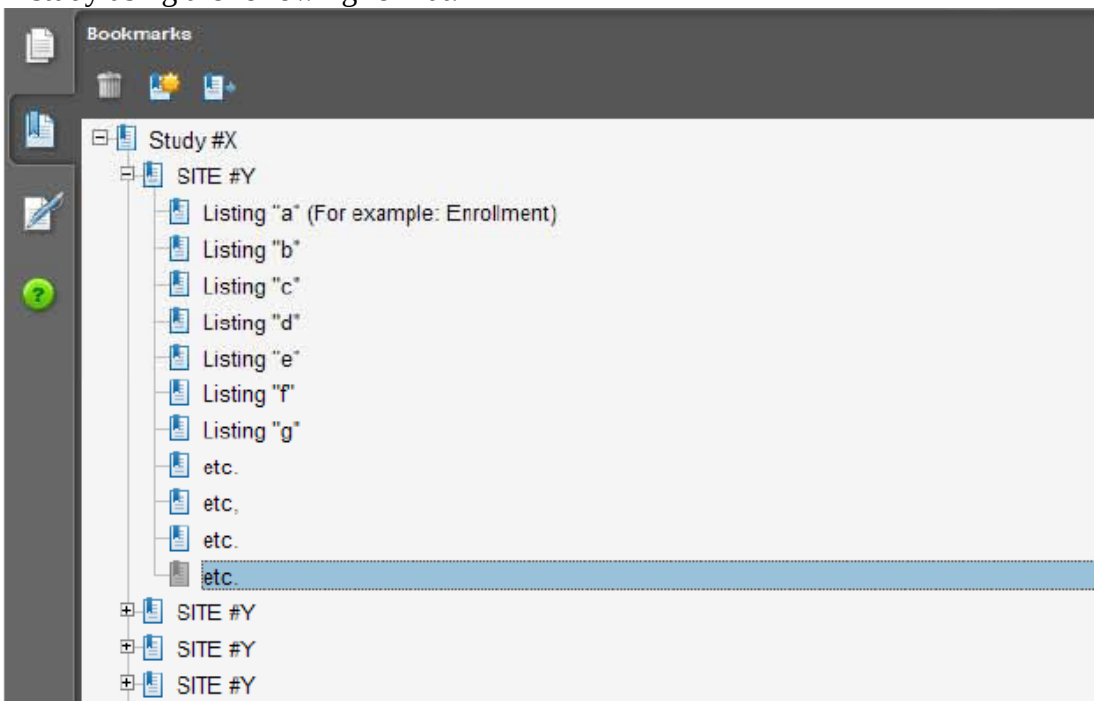
4. For each pivotal trial provide a sample annotated Case Report Form (if items are provided elsewhere in submission, please describe location or provide a link to requested information).

5. For each pivotal trial provide original protocol and all amendments (if items are provided elsewhere in submission, please describe location or provide a link to requested information).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data ("line") listings. For each site provide line listings for:
   a. Listing for each subject/number screened and reason for subjects who did not meet eligibility requirements
   b. Subject listing for treatment assignment (randomization)
   c. Subject listing of drop-outs and subjects that discontinued with date and reason
   d. Evaluable subjects/ non-evaluable subjects and reason not evaluable
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of laboratory tests performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. Please refer to Attachment 1, "Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions" for further information. We request that you provide a dataset, as outlined, which includes requested data for each pivotal study submitted in your application.

Attachment 1

1 Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions

1.1 Introduction

The purpose of this pilot for electronic submission of a single new clinical site dataset is to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process in support of the evaluation of data integrity.

1.2 Description of the Summary level clinical site dataset

The summary level clinical site data are intended (1) to clearly identify individual clinical investigator sites within an application or supplement, (2) to specifically reference the studies to which those clinical sites are associated, and (3) to present the characteristics and outcomes of the study at the site level.

For each study used to support efficacy, data should be submitted by clinical site and treatment arm for the population used in the primary analysis to support efficacy. As a result, a single clinical site may contain multiple records depending on the number of studies and treatment arms supported by that clinical site.

The site-level efficacy results will be used to support site selection to facilitate the evaluation of the application. To this end, for each study used to support efficacy, the summary level clinical site dataset submission should include site-specific efficacy results by treatment arm and the submission of site-specific effect sizes.

The following paragraphs provide additional details on the format and structure of the efficacy related data elements.

Site-Specific Efficacy Results

For each study and investigator site, the variables associated with efficacy and their variable names are:

- Treatment Efficacy Result (TRTEFFR) – the efficacy result for each primary endpoint, by treatment arm (see below for a description of endpoint types and a discussion on how to report this result)
- Treatment Efficacy Result Standard Deviation (TRTEFFS) – the standard deviation of the efficacy result (treatEffR) for each primary endpoint, by treatment arm
- Site-specific Efficacy Effect Size (SITEEFFE) – the effect size should be the same representation as reported for the primary efficacy analysis
- Site-specific Efficacy Effect Size Standard Deviation (SITEEFFS) – the standard deviation of the site-specific efficacy effect size (SITEEFFE)

- Endpoint (endpoint) – a plain text label that describes the primary endpoint as described in the Define file data dictionary included with each application.
- Treatment Arm (ARM) – a plain text label for the treatment arm that is used in the Clinical Study Report.

In addition, for studies whose primary endpoint is a time-to-event endpoint, include the following data element:

- Censored Observations (CENSOR) –the number of censored observations for the given site and treatment.

If a study does not contain a time-to-event endpoint, record this data element as a missing value.

To accommodate the variety of endpoint types that can be used in analyses please reference the below endpoint type definitions when tabulating the site-specific efficacy result variable by treatment arm, "TRTEFFR."

- Discrete Endpoints – endpoints consisting of efficacy observations that can take on a discrete number of values (e.g., binary, categorical). Summarize discrete endpoints by an event frequency (i.e., number of events), proportion of events, or similar method at the site for the given treatment.
- Continuous Endpoints – endpoints consisting of efficacy observations that can take on an infinite number of values. Summarize continuous endpoints by the mean of the observations at the site for the given treatment.
- Time-to-Event Endpoints – endpoints where the time to occurrence of an event is the primary efficacy measurement. Summarize time-to-event endpoints by two data elements: the number of events that occurred (TRTEFFR) and the number of censored observations (CENSOR).
- Other – if the primary efficacy endpoint cannot be summarized in terms of the previous guidelines, a single or multiple values with precisely defined variable interpretations should be submitted as part of the dataset.

In all cases, the endpoint description provided in the "endpoint" plain text label should be expressed clearly to interpret the value provided in the (TRTEFFR) variable.

The site efficacy effect size (SITEEFFE) should be summarized in terms of the primary efficacy analysis (e.g., difference of means, odds ratio) and should be defined identically for all records in the dataset regardless of treatment.

The Define file for the dataset is presented in Exhibit 1: *Table 1 Clinical Site Data Elements Summary Listing (DE)*. A sample data submission for the variables identified in Exhibit 1 is provided in Exhibit 2. The summary level clinical site data can be submitted in SAS transport file format (*.xpt).

Exhibit 1: Table 1 Clinical Site Data Elements Summary Listing (DE)

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
1	STUDY	Study Number	Char	String	Study or trial identification number.	ABC-123
2	STUDYTL	Study Title	Char	String	Title of the study as listed in the clinical study report (limit 200 characters)	Double blind, randomized placebo controlled clinical study on the influence of drug X on indication Y
3	DOMAIN	Domain Abbreviation	Char	String	Two-character identification for the domain most relevant to the observation. The Domain abbreviation is also used as a prefix for the variables to ensure uniqueness when datasets are merged.	DE
4	SPONNO	Sponsor Number	Num	Integer	Total number of sponsors throughout the study. If there was a change in the sponsor while the study was ongoing, enter an integer indicating the total number of sponsors. If there was no change in the sponsor while the study was ongoing, enter “1”.	1
5	SPONNAME	Sponsor Name	Char	String	Full name of the sponsor organization conducting the study at the time of study completion, as defined in 21 CFR 312.3(a).	DrugCo, Inc.
6	IND	IND Number	Num	6 digit identifier	Investigational New Drug (IND) application number. If study not performed under IND, enter -1.	010010
7	UNDERIND	Under IND	Char	String	Value should equal "Y" if study at the site was conducted under an IND and "N" if study was not conducted under an IND (i.e., 21 CFR 312.120 studies).	Y
8	NDA	NDA Number	Num	6 digit identifier	FDA new drug application (NDA) number, if available/applicable. If not applicable, enter -1.	021212
9	BLA	BLA Number	Num	6 digit identifier	FDA identification number for biologics license application, if available/applicable. If not applicable, enter -1.	123456
10	SUPPNUM	Supplement Number	Num	Integer	Serial number for supplemental application, if applicable. If not applicable, enter -1.	4
11	SITEID	Site ID	Char	String	Investigator site identification number assigned by the sponsor.	50
12	ARM	Treatment Arm	Char	String	Plain text label for the treatment arm as referenced in the clinical study report (limit 200 characters).	Active (e.g., 25mg), Comparator drug product name (e.g., Drug x), or Placebo
13	ENROLL	Number of Subjects Enrolled	Num	Integer	Total number of subjects enrolled at a given site by treatment arm.	20
14	SCREEN	Number of Subjects Screened	Num	Integer	Total number of subjects screened at a given site.	100

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
15	DISCONT	Number of Subject Discontinuations	Num	Integer	Number of subjects discontinuing from the study after being enrolled at a site by treatment arm as defined in the clinical study report.	5
16	ENDPOINT	Endpoint	Char	String	Plain text label used to describe the primary endpoint as described in the Define file included with each application (limit 200 characters).	Average increase in blood pressure
17	ENDPTYPE	Endpoint Type	Char	String	Variable type of the primary endpoint (i.e., continuous, discrete, time to event, or other).	Continuous
18	TRTEFFR	Treatment Efficacy Result	Num	Floating Point	Efficacy result for each primary endpoint by treatment arm at a given site.	0, 0.25, 1, 100
19	TRTEFFS	Treatment Efficacy Result Standard Deviation	Num	Floating Point	Standard deviation of the efficacy result (TRTEFFR) for each primary endpoint by treatment arm at a given site.	0.065
20	SITEEFFE	Site-Specific Efficacy Effect Size	Num	Floating Point	Site effect size with the same representation as reported for the primary efficacy analysis.	0, 0.25, 1, 100
21	SITEEFFS	Site-Specific Efficacy Effect Size Standard Deviation	Num	Floating Point	Standard deviation of the site-specific efficacy effect size (SITEEFFE).	0.065
22	CENSOR	Censored Observations	Num	Integer	Number of censored observations at a given site by treatment arm. If not applicable, enter -1.	5
23	NSAE	Number of Non-Serious Adverse Events	Num	Integer	Total number of non-serious adverse events at a given site by treatment arm. This value should include multiple events per subject and all event types (i.e., not limited to only those that are deemed related to study drug or treatment emergent events).	10
24	SAE	Number of Serious Adverse Events	Num	Integer	Total number of serious adverse events excluding deaths at a given site by treatment arm. This value should include multiple events per subject.	5
25	DEATH	Number of Deaths	Num	Integer	Total number of deaths at a given site by treatment arm.	1
26	PROTVIOL	Number of Protocol Violations	Num	Integer	Number of protocol violations at a given site by treatment arm as defined in the clinical study report. This value should include multiple violations per subject and all violation type (i.e., not limited to only significant deviations).	20
27	FINLMAX	Maximum Financial Disclosure Amount	Num	Floating Point	Maximum financial disclosure amount ($USD) by any single investigator by site. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	20000.00
28	FINLDISC	Financial Disclosure Amount	Num	Floating Point	Total financial disclosure amount ($USD) by site calculated as the sum of disclosures for the principal investigator and all sub-investigators to include all required parities. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	25000.00

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
29	LASTNAME	Investigator Last Name	Char	String	Last name of the investigator as it appears on the FDA 1572.	Doe
30	FRSTNAME	Investigator First Name	Char	String	First name of the investigator as it appears on the FDA 1572.	John
31	MINITIAL	Investigator Middle Initial	Char	String	Middle initial of the investigator, if any, as it appears on the FDA 1572.	M
32	PHONE	Investigator Phone Number	Char	String	Phone number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
33	FAX	Investigator Fax Number	Char	String	Fax number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
34	EMAIL	Investigator Email Address	Char	String	Email address of the primary investigator.	john.doe@mail.com
35	COUNTRY	Country	Char	ISO 3166-1-alpha-2	2 letter ISO 3166 country code in which the site is located.	US
36	STATE	State	Char	String	Unabbreviated state or province in which the site is located. If not applicable, enter NA.	Maryland
37	CITY	City	Char	String	Unabbreviated city, county, or village in which the site is located.	Silver Spring
38	POSTAL	Postal Code	Char	String	Postal code in which site is located. If not applicable, enter NA.	20850
39	STREET	Street Address	Char	String	Street address and office number at which the site is located.	1 Main St, Suite 100

The following is a fictional example of a data set for a placebo-controlled trial. Four international sites enrolled a total of 205 subjects who were randomized in a 1:1 ratio to active or placebo. The primary endpoint was the percent of responders. The site-specific efficacy effect size (SITEEFFE) is the difference between the active and the placebo treatment efficacy result. Note that since there were two treatment arms, each site contains 2 rows in the following example data set and a total of 8 rows for the entire data set.

Exhibit 2: Example for Clinical Site Data Elements Summary Listing (Table 1)

STUDY	STUDYTL	DOMAIN	SPONNO	SPONNAME	IND	UNDERIND	NDA	BLA	SUPPNUM	SITEID	ARM	ENROLL	SCREEN	DISCONT
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Active	26	61	3
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Placebo	25	61	4
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Active	23	54	2
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Placebo	25	54	4
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Active	27	62	3
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Placebo	26	62	5
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Active	26	60	2
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Placebo	27	60	1

ENDPOINT	ENDTYPE	TRTEFFR	TRTEFFS	SITEEFFE	SITEEFFS	CENSOR	NSAE	SAE	DEATH	PROTVIOL	FINLMAX	FINLDISC	LASTNAME	FRSTNAME
Percent Responders	Binary	0.48	0.0096	0.34	0.0198	-1	0	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.14	0.0049	0.34	0.0198	-1	2	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.48	0.0108	0.33	0.0204	-1	3	2	1	0	45000.00	45000.00	Washington	George
Percent Responders	Binary	0.14	0.0049	0.33	0.0204	-1	0	2	0	3	20000.00	45000.00	Washington	George
Percent Responders	Binary	0.54	0.0092	0.35	0.0210	-1	2	2	0	1	15000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.19	0.0059	0.35	0.0210	-1	3	6	0	0	22000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.46	0.0095	0.34	0.0161	-1	4	1	0	0	0.00	0.00	Lincoln	Abraham
Percent Responders	Binary	0.12	0.0038	0.34	0.0161	-1	1	2	0	1	0.00	0.00	Lincoln	Abraham

MINITIAL	PHONE	FAX	EMAIL	COUNTRY	STATE	CITY	POSTAL	STREET
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.

Attachment 2

Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1 (http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

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/s/

NORMAN L STOCKBRIDGE
09/05/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 109771

MEETING PRELIMINARY COMMENTS

Forest Laboratories, Inc.
Attention: Peter Karlton
Director, Regulatory Affairs CMC
Harborside Financial Center Plaza V, Suite 1900
Jersey City, NJ 07311

Dear Mr. Karlton:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Nebivolol/Valsartan Fixed Dose.

We also refer to your March 19, 2013, correspondence, requesting a meeting to discuss the [redacted] (b) (4) strategy for submitting stability data to the NDA.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me, at (301) 796-2133.

Sincerely,

{See appended electronic signature page}

Yvonne Knight
Regulatory Health Project Manager
Division of New Drug Quality Assessment I
Office of New Drug Evaluation
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: Guidance

Meeting Date and Time: May 21, 2013, 3:00 PM – 4:00 PM (EST)
Meeting Location: Teleconference

Application Number: 109771
Product Name: Nebivolol/Valsartan Fixed Dose Combination.
Indication: Treatment of hypertension
Sponsor/Applicant Name: Forest Laboratories, Inc.

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for May 21, 2013, 3:00 PM – 4:00 PM (EST) between **Forest Laboratories, Inc**. **and the Office of New Drug Quality Assessment.** We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager Yvonne Knight). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. **Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible**. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

1.0 BACKGROUND

The purpose of this type B, pre-NDA CMC meeting is to discuss [redacted] (b) (4) the strategy for timing the submission of stability data in the NDA.

Forest Research Institute, Inc. is planning on submitting a NDA for a fixed-dose combination (FDC) tablet consisting of Nebivolol and valsartan for the treatment of hypertension. Nebivolol is a beta blocker approved for the treatment of hypertension in the United States (Bystolic®); NDA 21-742. Valsartan is an angiotensin receptor blocker also approved in the United States for the treatment of hypertension

In Forest's on-going Phase III pivotal efficacy study (NAC-MD-01), five FDCs of Nebivolol and valsartan (5mg/80mg, 5mg/160mg, 10mg/160mg, 10mg/320mg and 20mg/320 mg) are currently being evaluated. [redacted] (b) (4)

Forest Laboratories, Inc. would like to [redacted] (b) (4) gain concurrence that they may submit the [redacted] (b) (4) stability [redacted] (b) (4) within 30 calendar days of the NDA submission

2. DISCUSSION

2.1. Chemistry, Manufacturing and Controls

Question 1: *Based on compositional and dissolution similarities, as well as the clinical data presented in our briefing book, does the Agency agree that Forest's strategy* [redacted] (b) (4) *will be acceptable?*

FDA Response to Question 1: Pending NDA review, your proposed strategy for [redacted] (b) (4) **your proposed Nebivolol/Valsartan FDC is appropriate. Be sure to include in your NDA,** [redacted] (b) (4) **all supporting data and justifications.** [redacted] (b) (4)

Reference ID: 3309923

Question 2: *Forest intends to submit the NDA with 12 months of stability data on a bottle configuration* (b) (4) *Does the agency concur with this proposal?*

FDA Response to Question 2: The Agency concurs with this proposal.

Reference ID: 3309923

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

/s/

REBECCA A MCKNIGHT
05/16/2013