

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206302Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 206302	NDA Supplement #: S- N/A	Efficacy Supplement Type SE- N/A
Proprietary Name: Byvalson Established/Proper Name: nebivolol/valsartan FDC Dosage Form: tablets Strengths: 5 mg/80 mg		
Applicant: Forest Laboratories, Inc		
Date of Receipt: 29 September 2015		
PDUFA Goal Date: 29 June 2016		Action Goal Date (if different): 3 June 2016
RPM: Bridget Kane, MS		
Proposed Indication(s): treatment of hypertension		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
NDA 021283 "Diovan"	Boxed Warning Indications and Usage Dosage and Administration Contraindications Warnings and Precautions Adverse Reactions Drug Interactions Use in Specific Populations Overdose Description Clinical Pharmacology Nonclinical Toxicology Clinical Studies Patient Counseling Information Patient Package Insert

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature¹. [See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.](#)

BA/BE studies (NAC-PK-04, NAC-PK-05 and NAC-PK-07)

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES NO
If "NO," proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If “**NO**”, proceed to question #5.
 If “**YES**”, list the listed drug(s) identified by name and answer question #4(c).

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?
 YES NO

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?
 YES NO
 If “**NO**,” proceed to question #10.

6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Diovan	NDA 021283	Yes

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?
 N/A YES NO
If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer “N/A”.
*If “**NO**”, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:
 a) Approved in a 505(b)(2) application?
 YES NO
 If “**YES**”, please list which drug(s).
 Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?
 YES NO
 If “**YES**”, please list which drug(s).
 Name of drug(s) approved via the DESI process:

c) Described in a final OTC drug monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing: **Diovan (NDA 020665)**

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application is for a new fixed dose combination containing Diovan.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

(Pharmaceutical equivalents are drug products in identical dosage forms intended for the same route of administration that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

*If "NO" to (a) proceed to question #11.
If "YES" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A YES NO

*If this application relies only on non product-specific published literature, answer "N/A"
If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO

If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A YES NO

If this application relies only on non product-specific published literature, answer "N/A"

If **“YES”** and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If **“NO”** or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): 5972990; 5972990*PED; 6294197; 6294197*PED

No patents listed proceed to question #14

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If **“NO”**, list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the

application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

- (a) Patent number(s): **6294197**
- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?
YES NO

If "NO", please contact the applicant and request the signed certification.

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.
YES NO

If "NO", please contact the applicant and request the documentation.

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): **27 May 2014**

Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information UNLESS the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

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/s/

BRIDGET E KANE
06/03/2016



DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Regulatory Project Manager Review

NDA: 206302
Drug: BYVALSON (nebivolol/valsartan) 5 mg/80 mg tablet
Class: Anti-hypertensive
Applicant: Forest Laboratories

Indication: (abbreviated) BYVALSON (nebivolol/valsartan) is a beta adrenergic blocker and an angiotensin II receptor blocker (ARB) indicated for the treatment of hypertension, to lower blood pressure. BYVALSON may be used alone or in combination with other antihypertensive agents.

Originally submitted: 24 February 2014
Date of resubmission: 29 September 2015
Approval date: 03 June 2016
PDUFA date: 29 June 2016

❖ **REVIEW TEAM**

- Office of New Drugs, Office of Drug Evaluation I, Division of Cardiovascular & Renal Products
 - Norman Stockbridge, MD, PhD (Director)
 - Aliza Thompson, MD (Clinical Team Leader)
 - Shen Xiao, MD (Clinical Reviewer)
 - Thomas Papoian, PhD (Non-clinical Team Leader)
 - Phillip Gatti, PhD (Non-clinical)
 - Michael Monteleone, MS, RAC (Associate Director of Labeling)
 - Bridget Kane, MS (Regulatory Health Project Manager)
- Office of Clinical Pharmacology
 - Rajnikanth Madabushi, PhD (Cross-Disciplinary Team Leader)
 - Martina Sahre, PhD (Reviewer)
 - Bilal AbuAsal, PhD (Reviewer)
- Office of Biostatistics, Division of Biometrics I
 - Hsien Ming J Hung, PhD (Director)
 - George Kordzakhia, PhD (Reviewer)
- Office of Product Quality
 - Wendy Wilson-Lee, PhD (Branch Chief)
 - Rao Kambhampati, PhD (CMC Reviewer)
 - Vibhakar Shah, PhD (CMC Reviewer)
 - Thuy Nguyen, PhD (Facilities)
 - Erika Pfeilder, PhD (Microbiology)
 - Houda Mahayni, PhD (Biopharmaceutics)
- Office of Surveillance and Epidemiology
 - Sarah Thomas, PharmD (DMEPA)

- Grace Jones, PharmD, BCPS (DMEPA)
- Office of Medical Policy
 - Office of Prescription Drug Promotion (OPDP)
 - Zama Patel, PharmD
 - Patient Labeling Team
 - Nyedra Booker, PharmD, MPH
- Division of Pediatric and Maternal Health
 - Miriam Dinatale, DO (Labeling review)

❖ **BACKGROUND**

NDA 206302 was submitted pursuant to section 505(b)(2) of the FD&C act and was received by the Division of Cardiovascular and Renal Products (the Division) on 24 February 2014 and filed on April 25, 2014. The applicant sought approval of a fixed dose combination (FDC) tablet in 5mg/80mg, 5mg/160mg, 10mg/160mg, 10mg/320mg, and 20mg/320mg strengths for the indication of the treatment of hypertension. The application was given a Standard review with a PDUFA goal of 24 December 2014. During the first review cycle, bioequivalence and clinical inspections were conducted and the data from the respective studies were found to be reliable. This application was discussed at an Advisory Committee meeting on 9 September 2014 with a resultant vote of 6-4 against approval.

On 24 December 2014, the Division issued a Complete Response letter stating that the observed anti-hypertensive effect of nebivolol/valsartan FDC was too small, compared to the effect achievable with the individual agents, and a safety advantage over monotherapy had not been demonstrated. The applicant was advised that the Division would consider evidence that Byvalson at sub-maximal doses are as additive as other combinations that are mechanistically independent and perhaps mitigate dose-related adverse reactions of either drug. This paradigm represents a novel approach for approving FDC antihypertensives.

On 30 June 2015, the applicant met with the Division to discuss their proposed response to the Complete Response. During the meeting, the Division confirmed that the magnitude of the treatment differences between the fixed dose combination (FDC) (b) (4) dose and the respective nebivolol and valsartan monotherapies was sufficient to support a resubmission. Subsequently, the applicant resubmitted this application on 29 September 2015 and the Division considered the resubmission complete and acknowledged it as a Class 2 resubmission on 26 October 2015 with a PDUFA goal date of 29 March 2016.

During the review, the review team was not convinced that the proposed dose (b) (4) met the criteria for an approvable dose based on the new paradigm. The Division requested additional information from the applicant to justify the advantage of the (b) (4) dose over the 5 mg/80 mg dose. After review of this information and further discussions with the applicant, the Division concluded that the 5 mg/80 mg dose should be approved. The review team did not feel that the (b) (4) dose provided any meaningful increases in blood pressure reduction or safety advantage when compared with the 5 mg/80 mg dose. The applicant submitted updated information to support the approval of this dose on 11 March 2016. This Division considered this information to be a major amendment on 17 March 2016 and the PDUFA goal was extended to 29 June 2016.

❖ **REGULATORY TIMELINE**

- Pre-IND meeting: 15 February 2011
- IND submitted: 27 May 2011
- Pre-NDA (CMC): 16 May 2013
- Pre-NDA meeting: 5 September 2013
- Original NDA submitted: 24 February 2014

- Filing meeting: 3 April 2014
- NDA filed: 25 April 2014
- 74 day letter issued: 6 May 2014
- Mid-cycle meeting: 28 July 2014
- Advisory Committee Meeting: 09 September 2014
- 505(b)(2) committee cleared: 10 November 2014
- PDUFA date: 24 December 2014
- Complete Response issued: 24 December 2014
- Type B meeting: 30 June 2015
- Class 2 Resubmission: 29 September 2015
- Response to Information Request received: 23 February 2016 (dose rationale)
- 505(b)(2) committee cleared: 30 April 2016
- Response to Information Request received: 11 March 2016 (CMC info. related to 5/80 dosage)
- Major Amendment: 17 March 2016
- Original PDUFA Date: 29 March 2016
- Post Major Amendment PDUFA Date: 29 June 2016
- Approval Letter: 02 June 2016

User Fee

The user fee for this application was paid in full on 4 February 2014, prior to the submission of the application (ID 3013947).

Pediatric Review Committee (PeRC)

The PeRC meeting to discuss this application was held on 17 December 2014. The PeRC and the Division agreed with the applicant that Byvalson is unlikely to be used in a substantial number of pediatric patients. This product is a combination antihypertensive agent. There are single agent products studied and labeled for use in pediatrics, and most pediatric patients are not routinely treated with combination antihypertensives. Therefore, a full pediatric waiver was granted for this application.

Advisory Committee

An advisory committee meeting was held on 9 September 2014 to discuss the effect size of the FDC and whether this effect size was supportive of approval. As stated above, the committee voted 6-4 against approval of the FDC.

Trade name

BYVALSON was deemed conditionally acceptable on 22 August 2014 (first review cycle) and again on 22 December 2015 (resubmission).

Review Status

This application was considered a Standard review during the first review cycle. The resubmission was considered a Class 2 resubmission.

Facilities

The Office of Compliance issued an Overall Approval recommendation for this application on 15 April 2014; verified on 21 July 2014 for the first review cycle. The facilities were found to be acceptable for the resubmission as verified by the facilities reviewer on 28 January 2016 and 1 May 2016.

❖ LABELING REVIEW

Labeling discussions began 7 March 2016 and were concluded on 25 May 2016. Please see the final label appended to the approval letter.

❖ **DISCIPLINE REVIEWS (Resubmission)**

Below are the conclusions reached by the review team members, organized by role and/or discipline.

Class 2 Resubmission

Divisional/CDTL Memorandum (24 May 2016 – Stockbridge, Madabushi, Thompson)

A joint Division and CDTL memo conveys the Division's decision to approve this NDA on the basis that the nebivolol/valsartan FDC offers nearly additive benefits of two mechanistically independent antihypertensives with no increase in adverse effects.

Clinical/Statistical Joint Review (5 April 2016 – Xiao, Kordzakhia)

Recommended action: Approval

Drs. Xiao and Kordzakhia conducted a joint review and recommend approval of Byvalson 5 mg/80 mg based on analyses of the LS mean reduction from baseline in blood pressure, the cumulative distribution of the change from baseline in blood pressure, and the probability of achieving blood pressure targets by baseline blood pressure. Their analysis of the safety data indicated that this dosage of Byvalson was well-tolerated.

Clinical Pharmacology Review (29 March 2016 - Sahre)

Recommended action: Approval

Dr. Sahre recommended approval of the 5 mg/80 mg dose of Byvalson stating that the dose-response information for the monotherapies and the FDC provide the supportive evidence of effect for approval.

Office of Product Quality Review (3 May 2016 –Kambhampati, Wilson)

Recommended action: Approval

Please refer to review in Panorama.

Review Cycle 1

Division Director's Memo (23 December 2014)

In his memo, Dr. Stockbridge conveys the Division's decision to issue a Complete Response for this application citing the only approval issue as the effect size.

CDTL Memo (17 December 2014)

Recommended Action: Complete Response

In his review, Dr. Madabushi concludes that the benefits proffered with the FDC can be achieved with nebivolol monotherapy and that the FDC does not provide a tolerability advantage over nebivolol monotherapy. Dr. Madabushi cautions that approval of the FDC as a replacement therapy would only serve to legitimize a combination with weak mechanistic basis and unnecessarily delay patients from receiving other antihypertensive treatments that have greater treatment effects.

Clinical Review (7 August and 5 December 2014)

Recommended Action: Complete Response

In his review of August 7, 2014, Dr. Xiao summarizes that there are no safety findings that would preclude approval, but notes the small treatment effect of the fixed dose combination when compared to the highest approved dose of nebivolol. In his December 5, 2014 addendum, Dr. Xiao summarizes that based upon the discussion at the Advisory Committee as well as failed subsequent analysis by the applicant to identify a responder population; he does not recommend approval of the application. Dr.

Xiao notes again that the treatment effect is small, both in absolute terms and relative to the effect achieved with other marketed products, and expresses concern that approval of this product may delay and/or prevent patients from getting to blood pressure goal.

Statistical Review (1 August and 18 September 2014)

In his August 1, 2014 review, Dr. Kordzakhia concludes that based on the pre-specified primary statistical analysis, the fixed dose combination (FDC) 20/320 mg was statistically more effective than both the nebivolol 40 mg monotherapy and the valsartan 320 mg monotherapy as measured by mean reduction in diastolic blood pressure. Whether the observed treatment difference between FDC 20/320 mg and nebivolol 40 mg (equal to -1.2 mm Hg) can be considered clinically meaningful is uncertain.

Clinical Pharmacology (15 August 2014 – Sahre, Abu Asal)

Recommended Action: Approvable

Please see review for details.

Pharmacology Review (21 March 2014 – Gatti)

Recommended action: Approvable

Please see review for details.

Chemistry Reviews

CMC (24 October 2014 - Kambhampati)

Biopharmaceutics (24 October 2014 & 14 December 2014 – Mahayni)

Microbiology (28 May 2014 – Pfeiler)

Recommended Action: Approvable

In his review dated October 24, 2014, Dr. Kambhampati summarizes that from a CMC perspective the application is approvable, pending satisfactory review of the outstanding Biopharmaceutics issues. In her memo dated December 14, 2014, Dr. Mahayni recommended the application be approved from a Biopharmaceutics perspective.

❖ **CONSULT REVIEWS**

Please see the following reviews and their corresponding dates:

Class 2 Resubmission

- OSE/DMEPA: 23 March 2016; 22 February 2016; 19 January 2016;
- OPDP: 23 March 2016
- Patient Labeling (Medication Guide): 23 March 2016
- DPMH: 16 March 2016

Review Cycle 1

- OSE/DMEPA: 12 August 2014; 20 March 2014; 22 October 2014
- OSI: 5 September 2014
- BIMO: 22 October 2014

❖ **CONCLUSION**

After considering the primary reviews, consults, and the applicant's additional analyses related to the 5 mg/80 mg dose of Byvalson, the Agency issued an approval letter. This letter was prepared for signature on 2 June 2016 and signed by Dr. Norman Stockbridge, Division Director, for NDA 206302 on 3 June 2016.

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/s/

BRIDGET E KANE
06/03/2016

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: March 23, 2016

To: Bridget Kane, MS
Regulatory Health Project Manager
Division of Cardiovascular and Renal Products (DCRP)

From: Zarna Patel, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **BYVALSON (nebivolol/valsartan) tablets**
NDA: 206302
Comments on draft product labeling

OPDP has reviewed the proposed Package Insert (PI) submitted for consult on October 13, 2015, for BYVALSON (nebivolol/valsartan) tablets. OPDP's comments are provided directly on the attached copy of the proposed labeling emailed to us on March 15, 2016.

OPDP has also reviewed the Carton and Container Labeling submitted by the sponsor on March 11, 2016 and we have no additional comments at this time.

Thank you for the opportunity to comment on the proposed labeling.

If you have any questions, please contact Zarna Patel at 301.796.3822 or zarna.patel@fda.hhs.gov.

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/s/

ZARNA PATEL
03/23/2016

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: March 23, 2016

Requesting Office or Division: Division of Cardiovascular and Renal Products

Application Type and Number: NDA 206302

Product Name and Strength: Byvalson (Nebivolol and Valsartan) tablets, 5 mg/80 mg

Submission Dates: March 11, 2016 and March 15, 2016

Applicant/Sponsor Name: Forest Laboratories, LLC.

OSE RCM #: 2015-2260-2

DMEPA Primary Reviewer: Sarah Thomas, PharmD

DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD

1 PURPOSE OF MEMO

The Division of Cardiovascular and Renal Products (DCRP) requested that we review the revised container labels and carton labeling submitted on March 11, 2016 (Appendix A), as well as the prescribing information and patient information submitted on March 15, 2016 for Byvalson to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during previous label and labeling reviews,^{1,2,3} as well as a change in strength for Byvalson tablets (b) (4) to 5 mg/80 mg.

¹ Jones G. Label and Labeling Review for Byvalson (NDA 206302). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 Oct 22. 13 p. OSE RCM No.: 2014-506.

² Thomas S. Label and Labeling Review for Byvalson (NDA 206302). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 Jan 19. 9 p. OSE RCM No.: 2015-2260.

³ Thomas S. Label and Labeling Review for Byvalson (NDA 206302). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 Feb 12. 8 p. OSE RCM No.: 2015-2260-1.

2 CONCLUSION

Forest Laboratories, LLC. incorporated the majority of our recommendations from the previous reviews, with the exception of not specifically stating the maximum recommended dose in the prescribing information. We find the revised container labels and carton labeling acceptable from a medication error perspective.

3 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information Section 2, Dosage and Administration

1. Given that the proposed strength is now being switched (b) (4) to 5 mg/80 mg, we have this question: If desirable antihypertensive effects are not attained within 2 to 4 weeks, can the Byvalson dose be increased or should patients be switch to other antihypertensive agents? If the dose may be increased, then such dose increase instructions should be provided in the PI (e.g. dose range up to a maximum daily dose). If the dose may not be increased from 5 mg/80 mg given orally once daily, then consider providing instructions on what to do, or at the minimum provide the information that the maximum daily dose is 5 mg/80 mg so that prescribers will know there's no dose adjustment.

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/s/

SARAH E THOMAS
03/23/2016

CHI-MING TU
03/23/2016

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: March 23, 2016

To: Norman Stockbridge, MD, PhD
Director
Division of Cardiovascular and Renal Products (DCaRP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
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From: Nyedra W. Booker, PharmD, MPH
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Division of Medical Policy Programs (DMPP)

Zarna Patel, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): BYVALSON (nebivolol/valsartan)

Dosage Form and Route: tablets

Application Type/Number: NDA 206302

Applicant: Forest Research Institute, Inc.

1 INTRODUCTION

On September 29, 2015 Forest Research Institute, Inc. re-submitted for the Agency's review a 505(b)(2) New Drug Application (NDA) 206302 for BYVALSON (nebivolol/valsartan), tablets. The Division of Cardiovascular and Renal Products (DCaRP) considers the Applicant's submission to be a complete, class 2 response to the Agency's Complete Response Letter issued on December 24, 2014. The proposed indication for BYVALSON (nebivolol/valsartan), tablets is for the treatment of hypertension, to lower blood pressure.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the DCaRP on October 13, 2015 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for BYVALSON (nebivolol/valsartan), tablets.

2 MATERIAL REVIEWED

- Draft BYVALSON (nebivolol/valsartan), tablets PPI received on September 29, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 15, 2016.
- Draft BYVALSON (nebivolol/valsartan), tablets Prescribing Information (PI) received on September 29, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 15, 2016.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

NYEDRA W BOOKER
03/23/2016

ZARNA PATEL
03/23/2016

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03/23/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Division of Pediatric and Maternal Health Memorandum

Date: March 14, 2016 **Date Consulted:** January 7, 2016

From: Miriam Dinatale, D.O., Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health
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Lynne P. Yao, MD, Director
Division of Pediatric and Maternal Health

To: Division of Cardiovascular and Renal Products (DCRP)

Drug: BYVALSON (nebivolol/valsartan) tablets

NDA: 206302

Applicant: Forest Laboratories, LLC

Subject: Pregnancy and Lactation Labeling

**Proposed
Indication:** Treatment of hypertension

**Materials
Reviewed:**

- DPMH consult request for NDA 206302, Byvalson (nebivolol/valsartan). January 7, 2016, DARRTS Reference ID 3870734.
- Applicant's submitted background package for NDA 206302, Byvalson (nebivolol/valsartan).
- Division of Pediatric and Maternal Health Review of [REDACTED] (b) (4) NDA 206302. M. Dinatale, D.O. May 26, 2015. DARRTS Reference ID 3764048.

- Division of Cardiovascular and Renal Products Clinical Review of Nebivolol/Valsartan, NDA 206302. S. Xiao, M.D., Ph.D. August 7, 2014. DARRTS Reference ID 3606074.

Consult Question:

DCRP requests assistance from DPMH to “review the label to ensure that it meets PLLR format.”

INTRODUCTION

The Division of Cardiovascular and Renal Products (DCRP) consulted the Division of Pediatric and Maternal Health (DPMH) on January 7, 2016, to provide input for appropriate format and content of the pregnancy and lactation subsections of Byvalson (nebivolol/valsartan) labeling to be in compliance with the Pregnancy and Lactation Labeling Rule.

REGULATORY HISTORY

- On February 24, 2014, Forest Laboratories, LLC, submitted a 505 (b)(2) New Drug Application (NDA) for Byvalson (nebivolol/valsartan), NDA 206302, for the proposed indication of treatment of hypertension. Nebivolol (Bystolic) was approved in the U.S. in 2007 for the treatment of hypertension (as monotherapy or in combination with other antihypertensive agents). Valsartan (Diovan) was approved in the U.S. in 1996 and is indicated for the treatment of hypertension (as monotherapy or in combination with other antihypertensive agents) and heart failure.
- On September 9, 2014, the DCRP Advisory Committee met to discuss Byvalson, and the committee did not reach a unanimous decision in determining whether or not the drug would be approved. DCRP noted that Byvalson’s effect was small and a safety advantage over other anti-hypertensive agents had not been demonstrated. FDA issued a Complete Response (CR) letter to the applicant on December 24, 2014.¹
- Forrest Laboratories, LLC provided a response to the CR on September 29, 2015.

BACKGROUND**Nebivolol/Valsartan and Drug Characteristics**

Nebivolol is a beta-adrenergic blocking agent, which works to decrease heart rate, decrease myocardial contractility, decrease sympathetic activity, and suppress renin activity and results in vasodilation and a decrease in peripheral vascular resistance. Nebivolol has a molecular weight of 441.9 g/mol, protein-binding of 98%, and a half-life of 12 to 19 hours. Adverse reactions that have been seen in clinical trials and in post-marketing reports include: bronchospasm, bradycardia, atrioventricular block, and hypotension.

Valsartan is an angiotensin II receptor blocker with effects that block the vasoconstrictor and aldosterone-secreting effects of angiotensin II. Valsartan has a molecular weight of 435.52 g/mol, protein-binding of 95%, bioavailability of 25%, and a half-life of six hours. Adverse reactions that have been seen in clinical trials and in post-marketing reports include: angioedema, cough, renal failure, hepatitis, hypotension, and hyperkalemia.

¹ DCRP Complete Response Letter Norman Stockbridge, M.D., Ph.D. December 24, 2014. DARRTS Reference ID 3678260.

Cardiovascular Disease and Pregnancy

Chronic hypertension occurs in up to 5% of pregnant women. Pregnant women with hypertension are at an increased risk for preeclampsia (occurs in 13-40% of pregnant women with chronic hypertension), gestational diabetes (OR 1.8; 95% CI 1.4-2.0), cesarean delivery (OR 2.7; 95% CI 2.4-3.0), post-partum hemorrhage (OR 2.2, 95% CI 1.4-3.7), placental abruption, premature delivery, intrauterine growth restriction, and intrauterine death.^{2,3}

Current Labeling for Nebivolol and other Beta-Blockers

Current nebivolol labeling⁴ notes that there are no studies with nebivolol that have been conducted in pregnant women and to use nebivolol only if the potential benefit outweighs the risk to the fetus. Labeling for other beta-blockers, such as atenolol and labetalol, notes that infants born to mothers taking these beta-blockers are at risk for hypotension, bradycardia, hypoglycemia and respiratory depression.⁵

Current Labeling for Valsartan and other Angiotensin Receptor Blockers

Current valsartan labeling⁶ notes that use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and may result in fetal and neonatal morbidity (oligohydramnios with resulting fetal lung hypoplasia and skeletal deformations, anuria, hypotension, renal failure) and fetal death.

Pregnancy and Lactation Labeling

On December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the “*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,”⁷ also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule⁸ format to include information about the risks and benefits of using these products during pregnancy and lactation. The PLLR went into effect on June 30, 2015.

² The American College of Obstetrics and Gynecologist. Hypertension in Pregnancy. 2013. <http://www.acog.org/Resources-And-Publications/Task-Force-and-Work-Group-Reports/Hypertension-in-Pregnancy>. Accessed 1/29/2016.

³ NIH: National Heart, Lung, and Blood Institute. High Blood Pressure in Pregnancy. <http://www.nhlbi.nih.gov/health/resources/heart/hbp-pregnancy>. Accessed 1/29/2016.

⁴ Drugs@FDA: Bystolic (nebivolol). Use in Specific Populations (8.1). Accessed 3/14/2016.

⁵ Drugs@FDA: Tenormin (atenolol) and Trandate (labetalol). Accessed 1/29/2016.

⁶ Drugs@FDA: Diovan (valsartan). Warnings and Precautions: Fetal Toxicity (5.1). Accessed 3/14/2016.

⁷ *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

⁸ *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

REVIEW OF DATA

Nebivolol/Valsartan and Nonclinical Findings

Current Byvalson labeling provided by the applicant includes data from animal reproduction studies that were conducted for the initial approval of nebivolol and valsartan. No new nonclinical studies have been submitted with this NDA. Embryo-fetal and perinatal lethality have been observed when nebivolol was given to pregnant rats during organogenesis at doses 1.2-times the maximum recommended human dose (MRHD). No teratogenic effects were observed in pregnant mice and rats administered oral valsartan at doses up to 600mg/kg/day and to pregnant rabbits administered oral valsartan at doses up to 10mg/kg/day during organogenesis. The reader is referred to the current Nonclinical review by P. Gatti, Ph.D. for further details.

Nebivolol/Valsartan and Pregnancy

Clinical Trials

There were two pregnancies that were reported in study participants during the 8-week, double-blind treatment period. One patient was on placebo, and the other patient was on nebivolol/valsartan 10/320 mg. The narrative summary for the patient on treatment is as follows:

- The patient on nebivolol/valsartan was a 37 year-old female who started treatment on November 2, 2012. The patient's last menstrual period was on November 3, 2012. On December 14, 2012, the patient had a positive serum pregnancy test. Nebivolol/valsartan was stopped, and the patient was withdrawn from the study. The patient delivered a newborn male on [REDACTED] (b) (6) by normal vaginal delivery. The infant was diagnosed with trisomy 21. The mother's family history was significant for Down syndrome in a paternal cousin.

Two pregnancies were reported during the long-term open-label study. Both pregnancies occurred during the 52-week, open-label treatment phase. Their narratives are as follows:

- A 35 year-old female with a 4 year history of hypertension and obesity took nebivolol/valsartan from November 8, 2011 to February 20, 2012. Relevant concomitant medication included Cilest (ethinylestradiol and norgestimate), which was started in April 2011. The patient had a positive pregnancy test on February 27, 2012. On April 5, 2012, the patient developed hypothyroidism and gestational diabetes. On September 27, 2012, the patient developed cholestasis of pregnancy. On [REDACTED] (b) (6) the patient delivered a healthy male with a gestational age 34 weeks (preterm) with a birth weight of 6 lbs 1 oz and APGAR scores 9 at 1 and 5 minutes. There were no fetal malformations noted.
- A 35 year-old female with a 6 year history of hypertension and obesity received nebivolol/valsartan from November 29, 2011 to January 9, 2012. She was not taking any concomitant medications. The patient had a positive serum pregnancy test on January 10, 2012, and the drug was discontinued. The estimated gestational age at the time of the exposure was 3 weeks. The patient had a spontaneous abortion on [REDACTED] (b) (6) and no other information regarding any fetal malformations was provided.

The reader is referred to the DCRP review by S. Xiao, M.D. for further details of the pregnancies that were observed during clinical trials with nebivolol/valsartan.⁹

Applicant's Review of Published Literature

The applicant performed a search of published literature for available human pregnancy data for valsartan in PubMed, Medline, Embase, Embal, SciSearch, Biosis, HCAPlus, IPA, and DISSABS using the search terms: "valsartan and "pregnancy." There were no publications of clinical trials that evaluated the use of valsartan in pregnant women. However, there were 11 case study reports that described the use of valsartan in pregnant women. Based on the case reports, the applicant noted that valsartan use during the second and third trimester of pregnancy was associated with anhydramnios and oligohydramnios, observed via fetal ultrasound, and fetal malformations, such as skeletal deformations, respiratory distress and neonatal morbidity and mortality. In four women who had anhydramnios diagnosed between 20 to 28 weeks gestation, discontinuation of valsartan resulted in normalization of amniotic fluid volume within one to two weeks of discontinuing valsartan. Similar adverse effects were not observed in the six pregnant women who received valsartan only during the first trimester of pregnancy.¹⁰ The reader is referred to Appendix B for further details regarding the case reports that describe valsartan use during pregnancy. The applicant notes that the results of the case reports support current language that appears in section 8.1, Pregnancy.

DPMH's Review of Published Literature

Nebivolol

DPMH conducted a search of published literature in PubMed for available published data regarding nebivolol and use in pregnancy. One case study was found and is summarized below:

- A pregnant female was taking nebivolol 5mg/day for tachycardia during the last four months of her pregnancy. She delivered a full-term with a birth weight of 3040 grams. Twenty-four hours after birth, the infant developed hypoglycemia (blood glucose=30mg/dL), polycythemia (hematocrit 63.7%), hyponatremia (Sodium= 132), and jaundice (total bilirubin=12.5mg/dL) and was admitted to the neonatal intensive care unit. The infant's glucose and bilirubin normalized with treatment, and the infant was discharged at 10 days old. There were no fetal malformations that were noted.¹¹

In general, beta-blockers are commonly used to treat hypertension during pregnancy. While some studies that have evaluated the use of beta-blockers during pregnancy, have demonstrated an increased risk of intrauterine growth restriction, bradycardia, hypotension, hypoglycemia, respiratory distress and feeding problems^{12,13,14}, other studies have failed to demonstrate an

⁹ Division of Cardiovascular and Renal Products Review of Nebivolol/Valsartan, NDA 206302. S. Xiao, M.D., Ph.D. August 7, 2014. DARRTS Reference ID 3606074.

¹⁰ Byvalson. Efficacy Information Amendment. Forest Research Institute, Inc. January 29, 2016.

¹¹ Sullo, et al. Hypoglycemia, polycythemia and hyponatremia in a newborn exposed to nebivolol during pregnancy. *J Pharmacol Pharmacotherapy*. 2015; 6(1): 45-48.

¹² Lydakakis, et al. Atenolol and fetal growth in pregnancies complicated by hypertension. *Am J. Hypertension*. 1999; 12(6): 541-547.

¹³ Magee, et al. Oral beta-blockers for mild to moderate hypertension during pregnancy. *Cochrane Database Sys Reve*. 2003; 3.

¹⁴ Davis, et al. Risk of congenital malformations and perinatal among infants exposed to calcium channel and beta blockers during Pregnancy. *Pharmacoepidemiology and Drug Safety*. 2011; 20: 138-145.

increased risk for adverse fetal outcomes.^{15,16} Labeling for beta-blockers, such as atenolol and labetalol, notes that infants born to mothers taking these beta-blockers are at risk for hypotension, bradycardia, hypoglycemia and respiratory depression.¹⁷ DPMH recommends that similar language appear in the Clinical Considerations section of Byvalson labeling.

Valsartan

DPMH conducted a search of published literature in PubMed for available published data regarding valsartan and use in pregnancy. In addition to the case reports noted by the applicant above, there were no additional reports of valsartan use in pregnancy.

A review of TERIS¹⁸ demonstrates that fetal and neonatal morbidity (hypotension, hyperkalemia, oliguria, neonatal skull hypoplasia, anuria, renal failure) and death have been reported in several dozen cases of pregnant women who received drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy. There are also reports of spontaneous abortions, oligohydramnios and newborn renal dysfunction that have been reported with valsartan use in pregnant women. The occurrence of oligohydramnios is possibly due to decreased fetal renal function and has been associated with fetal limb contractures, craniofacial deformities, and hypoplastic lung development.

Summary

Although the applicant noted that there is no additional information to include in Byvalson labeling, the information about anhydramnios and improvement in amniotic fluid volume upon discontinuation of valsartan is not present in current labeling and will be added to Byvalson labeling.

Nebivolol/Valsartan and Lactation

Current Nebivolol and Valsartan Labeling

Current nebivolol labeling¹⁹ notes it is not known if nebivolol or its metabolites are present in human milk but due to the potential for serious adverse reactions (bradycardia), nebivolol is not recommended during breastfeeding.

Current valsartan labeling²⁰ notes that it is not known if valsartan is present in human milk but due to the potential for serious adverse reactions, valsartan is not recommended during breastfeeding.

¹⁵ Magee, et al. Fortnightly review: management of hypertension during pregnancy. Br Med J. 1999; 318 (7194): 1332-1336.

¹⁶ Easterling, et al. Prevention of preeclampsia: a randomized trial of atenolol in hyperdynamic patients before the onset of hypertension. Obstet Gynecol. 1993; 3 (5): 725-733.

¹⁷ Drugs@FDA. Tenormin (atenolol) and Trandate (labetalol). Accessed 1/29/2016.

¹⁸ TERIS is the TERatology Information Service located at University of Washington. It is an online database designed to assist physicians or other healthcare professionals in assessing the risks of possible teratogenic exposures in pregnant women. Review date 07/14. Accessed 5/15/15.

¹⁹ Drugs@FDA: Bystolic (nebivolol). Use in Specific Populations (8.2). Accessed 3/14/2016.

²⁰ Drugs@FDA: Diovan (valsartan). Use in Specific Populations (8.2). Accessed 3/14/2016.

Applicant's Review of Published Literature

The applicant performed a search of published literature for available human data for valsartan in PubMed, Medline, Embase, Embal, SciSearch, Biosis, HCAPlus, IPA, and DISSABS using the search terms: "valsartan" and "lactation." There were no clinical lactation studies or case reports that describe valsartan use in lactating women.

DPMH's Review of Published Literature

DPMH also conducted a review of published literature in PubMed and Embase, using the search terms "nebivolol," "valsartan," and "lactation/breastfeeding," and also reviewed data related to nebivolol and valsartan use during lactation in *Medications and Mother's Milk*²¹ and the Drugs and Lactation Database (LactMed).²²

There are no published data regarding nebivolol and valsartan use during lactation. In *Medications and Mother's Milk*, Dr. Hale, a breastfeeding expert, notes that there are no data available on the transfer of nebivolol into human breast milk, but due to the drug's high protein-binding and large volume of distribution, it is unlikely that nebivolol will be present in breast milk in clinically relevant amounts. However, due to the potential for beta blockers to cause bradycardia in the breastfeeding infant, Dr. Hale recommends that nebivolol not be used during breastfeeding. Dr. Hale notes that there are no data available on the transfer of valsartan into human breast milk and recommends that caution is used if valsartan is used during breastfeeding.

LactMed summarizes available nebivolol and valsartan lactation data as follows:

Because no information is available on the use of nebivolol or valsartan during breastfeeding, an alternate drug may be preferred, especially while nursing a newborn or preterm infant

In lactating rats, maximum milk levels of unchanged nebivolol were observed at 4 hours after single and repeat doses of 2.5 mg/kg/day. The daily dose (mg/kg body weight) ingested by a rat pup is 0.3% of the dam dose for unchanged nebivolol. For valsartan, the drug was detected in the milk of lactating rats 15 minutes to 4 hours after administration of a 3 mg/kg dose.

Summary

Although nebivolol and valsartan are transferred into rat milk, it is not known if nebivolol or valsartan are present in human milk. Both drugs have low molecular weights (nebivolol: 441.9g/mol and valsartan: 435.52g/mol), and nebivolol has a long half-life (12-19 hours)²³, which suggest that the drugs may be transferred into breast milk. Both drugs also have high protein binding (95%: valsartan, 98%: nebivolol), which decreases the presence of the drugs in

²¹ Hale, T. *Medications and Mother's Milk*. Hale Publishing, 2012.

²² <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

²³ Drugs with molecular weights (MW) greater than 800 Daltons are excluded from the milk compartment more readily than those with MWs less than 800 Daltons

*the mother's circulation and may decrease the transfer of the drugs into breastmilk, and consequently, infant exposure to the drugs via breast milk.*²⁴

Nevertheless, there are serious adverse reactions (see "Nebivolol/Valsartan and Drug Characteristics" above) that have been reported in adults who have taken valsartan and nebivolol, and DPMH agrees with the applicant that women should not breastfeed during treatment with Byvalson.

Nebivolol/Valsartan and Females and Males of Reproductive Potential

DPMH conducted a review of published literature in PubMed and Embase to evaluate the use of nebivolol and valsartan and their effects on fertility. No data were found.

There were effects on spermatogenesis in animal fertility studies with male rats and mice given oral nebivolol at 10 and 5-times, respectively, the MRHD. In rats, the effects on spermatogenesis were not reversible, and in mice, the effects on spermatogenesis were partially reversible. In a randomized, double-blind study with healthy males given nebivolol 10mg daily for six-weeks, there were no effects on serum luteinizing hormone or serum total testosterone.

In animal fertility studies in male and female rats given oral valsartan at doses 6-times the MRHD, there was no evidence of impaired fertility.²⁵

Summary

Current valsartan and nebivolol labels do not include information regarding contraception and pregnancy testing. Given the lack of new human data with valsartan and nebivolol and no evidence of first trimester fetal toxicity, DPMH recommends that information regarding pregnancy testing and contraception is not included in Byvalson labeling.

Although nebivolol had effects on spermatogenesis in male rats and mice, a study performed in humans did not result in similar findings. In addition, there is no evidence of infertility in animal studies with valsartan. Therefore, the "Infertility" subsection will not be included in section 8.3 of Byvalson labeling.

CONCLUSIONS

Byvalson (nebivolol/valsartan) labeling has been revised to comply with the PLLR. DPMH has the following recommendations for Byvalson labeling:

- **Warnings and Precautions, Section 5.10**
 - Based on the increased likelihood of fetal harm (anhydramnios and oligohydramnios), if angiotensin receptor blockers are used by pregnant women, a subsection describing embryo- and/or fetal risks ("Embryofetal Toxicity") as well as mitigation measures must be placed in the Warnings and Precautions section of Byvalson labeling as required by regulation (21 CFR 201.57(c)(9)(i)(A)(4)).

²⁴ Nice, F and Luo, Amy. Medications and breast-feeding: Current Concepts. Journal of the American Pharmacists Association. 2012; 51 (1): 86-94.

²⁵Current proposed labeling from Byvalson. Section 13, Nonclinical Toxicology.

- **Pregnancy, Section 8.1**
 - The “Pregnancy” subsection of Byvalson labeling was formatted in the PLLR format to include the “Risk Summary,” “Clinical Considerations,” and “Data” subsections.²⁶
- **Lactation, Section 8.2**
 - The “Lactation” subsection of Byvalson labeling was formatted in the PLLR format to include the “Risk Summary” and “Data” subsections.²⁷
- **Patient Counseling Information, Section 17**
 - The “Patient Counseling Information” section of Byvalson labeling was updated to correspond with changes made to sections 5.1, 8.1, and 8.2 of labeling.

RECOMMENDATIONS

DPMH revised subsections 5.1, 8.1, 8.2 and 17 in Byvalson labeling for compliance with the PLLR (see below). See Appendix A for the Applicant’s proposed labeling. DPMH refers to the final NDA action for final labeling.

²⁶ Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection A-8.1 Pregnancy, 2-Risk Summary.

²⁷ Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection, B- 8.2 Lactation, 1-Risk Summary.

DPMH Proposed Byvalson (nebivolol/valsartan) Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

<p style="text-align: center;">WARNING: FETAL TOXICITY <i>See full prescribing information for complete boxed warning.</i></p> <ul style="list-style-type: none">• When pregnancy is detected, discontinue BYVALSON as soon as possible. (5.1, 8.1)• Drugs, including BYVALSON, that act directly on the renin-angiotensin system can cause injury and death to the developing fetus. (5.1, 8.1)
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-----USE IN SPECIFIC POPULATIONS-----

- Lactation: Advise not to breastfeed. (8.2)

FULL PRESCRIBING INFORMATION

<p style="text-align: center;">WARNING: FETAL TOXICITY</p> <ul style="list-style-type: none">• When pregnancy is detected, discontinue BYVALSON as soon as possible. (5.1, 8.1)• Drugs, including BYVALSON, that act directly on the renin-angiotensin system can cause injury and death to the developing fetus (b) (4) (5.1, 8.1)

5 WARNINGS AND PRECAUTIONS

5.1 Fetal Toxicity

Valsartan

(b) (4)

Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. (b) (4)

When pregnancy is detected, (b) (4) discontinue BYVALSON as soon as possible [see *Use in Specific Populations* (8.1)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

BYVALSON (b) (4) can cause fetal harm when administered to a pregnant woman. Use of drugs that act on the renin-angiotensin system during second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Published reports include cases of anhydramnios and oligohydramnios in pregnant women treated with valsartan. (b) (4)

(b) (4)

When pregnancy is detected, consider alternative drug treatment and discontinue BYVALSON as soon as possible.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Hypertension in pregnancy increases the maternal risk for pre-eclampsia, gestational diabetes, premature delivery, and delivery complications (e.g., need for cesarean section, and post-partum hemorrhage). Hypertension increases the fetal risk for intrauterine growth restriction and intrauterine death. Pregnant women with hypertension should be carefully monitored and managed accordingly.

Fetal/Neonatal adverse reactions

Nebivolol

Neonates of women with hypertension, who are treated with beta-blockers during pregnancy, may be at increased risk for hypotension, bradycardia, hypoglycemia, and respiratory depression. Observe newborns for symptoms of hypotension, bradycardia, hypoglycemia and respiratory depression and manage accordingly.

Valsartan

Oligohydramnios in pregnant women who use drugs affecting the renin-angiotensin system in the second and third trimesters of pregnancy can result in the following: reduced fetal renal function leading to anuria and renal failure, fetal lung hypoplasia and skeletal deformations, including skull hypoplasia, hypotension, and death. In the unusual case that there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system for a particular patient, apprise the mother of the potential risk to the fetus.

In patients taking BYVALSON during pregnancy, perform serial ultrasound examinations to assess the intra-amniotic environment. Fetal testing may be appropriate, based on the week of gestation. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Closely observe infants with histories of *in utero* exposure to BYVALSON for hypotension, oliguria, and hyperkalemia. If oliguria or hypotension occur in neonates with a history of *in utero* exposure to BYVALSON, support blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and substituting for disordered renal function.

Data

Animal Data

No reproductive animal toxicity studies have been conducted with the combination of nebivolol and valsartan. Reproductive animal toxicity studies have been conducted for nebivolol and valsartan alone.

Nebivolol

Nebivolol was shown to increase embryo fetal and perinatal lethality in rats at approximately 1.2- times the maximum recommended human dose (MRHD) or 40 mg/day on a mg/m² basis. Decreased pup body weights occurred at 1.25 and 2.5 mg/kg in rats, when exposed during the

perinatal period (late gestation, parturition and lactation). At 5 mg/kg and higher doses (1.2-times the MRHD), prolonged gestation, dystocia and reduced maternal care were produced with corresponding increases in late fetal deaths and stillbirths and decreased birth weight, live litter size and pup survival. These events occurred only when nebivolol was given during the perinatal period (late gestation, parturition and lactation). Insufficient numbers of pups survived at 5 mg/kg to evaluate the offspring for reproductive performance.

In studies in which pregnant rats were given nebivolol during organogenesis, reduced fetal body weights were observed at maternally toxic doses of 20 and 40 mg/kg/day (5- and 10-times the MRHD), and small reversible delays in sternal and thoracic ossification associated with the reduced fetal body weights and a small increase in resorption occurred at 40 mg/kg/day (10-times the MRHD).

No adverse effects on embryo-fetal viability, sex, weight or morphology were observed in studies in which nebivolol was given to pregnant rabbits at doses as high as 20 mg/kg/day (10-times the MRHD).

Valsartan

No teratogenic effects were observed when valsartan was administered to pregnant mice and rats at oral doses up to 600 mg/kg/day and to pregnant rabbits at oral doses up to 10 mg/kg/day. However, significant decreases in fetal weight, pup birth weight, pup survival rate, and slight delays in developmental milestones were observed in studies in which parental rats were treated with valsartan at oral, maternally toxic (reduction in body weight gain and food consumption) doses of 600 mg/kg/day during organogenesis or late gestation and lactation. In rabbits, fetotoxicity (i.e., resorptions, litter loss, abortions, and low body weight) associated with maternal toxicity (mortality) was observed at doses of 5 and 10 mg/kg/day. The no observed adverse effect doses of 600, 200 and 2 mg/kg/day in mice, rats and rabbits represent 9-, 6-, and 0.1-times, respectively, the maximum recommended human dose on a mg/m² basis. Calculations assume an oral dose of 320 mg/day and a 60-kg patient.

8.2 Lactation

Risk Summary

There is no information regarding the presence of BYVALSON or its individual components in human milk, the effects on the breastfed infant, or the effects on milk production. Nebivolol and valsartan are present in rat milk [see Data]. Because of the potential (b) (4) and the potential for valsartan to affect postnatal renal development, in nursing infants, advise a nursing woman not to breastfeed during treatment with BYVALSON.

Data

In lactating rats, maximum milk levels of unchanged nebivolol were observed at 4 hours after single and repeat doses of 2.5 mg/kg/day. The daily dose (mg/kg body weight) ingested by a rat pup is 0.3% of the dam dose for unchanged nebivolol. For valsartan, the drug was detected in the milk of lactating rats 15 minutes to 4 hours after administration of a 3 mg/kg dose.

17 PATIENT COUNSELING INFORMATION

Fetal Toxicity

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to notify their healthcare provider with a known or suspected pregnancy [see *Warnings and Precautions (5.1) and Use in Specific Populations (8.1)*]

Lactation

Advise (b) (4) women not to breastfeed during treatment with BYVALSON [see *Use in Specific Populations (8.2)*].

PATIENT INFORMATION

WHO SHOULD NOT TAKE BYVALSON?

Do not take BYVALSON if you:

- (b) (4) .

WHAT SHOULD I TELL MY (b) (4) BEFORE TAKING BYVALSON?

(b) (4)

WHAT ARE POSSIBLE SIDE EFFECTS OF BYVALSON?

BYVALSON may cause (b) (4) serious side effects:

(b) (4)

APPENDIX A – Applicant’s Proposed Byvalson (nebivolol/valsartan) Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

-----USE IN SPECIFIC POPULATIONS-----

 (b) (4)

FULL PRESCRIBING INFORMATION

5 WARNINGS AND PRECAUTIONS

5.1 Fetal Toxicity

Valsartan

Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue valsartan as soon as possible [see *Use in Specific Populations (8.1)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: [see *Warnings and Precautions 5.1*]

Risk Summary

 (b) (4)

Clinical Considerations

 (b) (4)


[REDACTED] (b) (4)

[REDACTED] (b) (4)

Data

[REDACTED] (b) (4)

Animal

No reproductive animal toxicity studies have been conducted with the combination of nebivolol and valsartan. Reproductive animal toxicity studies have been conducted for nebivolol and valsartan alone.

Nebivolol

Nebivolol was shown to increase embryo fetal and perinatal lethality in rats at approximately 1.2 times the maximum recommended human dose (MRHD) or 40 mg/day on a mg/m² basis. Decreased pup body weights occurred at 1.25 and 2.5 mg/kg in rats, when exposed during the perinatal period (late gestation,

parturition and lactation). At 5 mg/kg and higher doses (1.2 times the MRHD), prolonged gestation, dystocia and reduced maternal care were produced with corresponding increases in late fetal deaths and stillbirths and decreased birth weight, live litter size and pup survival. These events occurred only when nebivolol was given during the perinatal period (late gestation, parturition and lactation). Insufficient numbers of pups survived at 5 mg/kg to evaluate the offspring for reproductive performance.

In studies in which pregnant rats were given nebivolol during organogenesis, reduced fetal body weights were observed at maternally toxic doses of 20 and 40 mg/kg/day (5 and 10 times the MRHD), and small reversible delays in sternal and thoracic ossification associated with the reduced fetal body weights and a small increase in resorption occurred at 40 mg/kg/day (10 times the MRHD).

No adverse effects on embryo-fetal viability, sex, weight or morphology were observed in studies in which nebivolol was given to pregnant rabbits at doses as high as 20 mg/kg/day (10 times the MRHD).

Valsartan

No teratogenic effects were observed when valsartan was administered to pregnant mice and rats at oral doses up to 600 mg/kg/day and to pregnant rabbits at oral doses up to 10

mg/kg/day. However, significant decreases in fetal weight, pup birth weight, pup survival rate, and slight delays in developmental milestones were observed in studies in which parental rats were treated with valsartan at oral, maternally toxic (reduction in body weight gain and food consumption) doses of 600 mg/kg/day during organogenesis or late gestation and lactation. In rabbits, fetotoxicity (i.e., resorptions, litter loss, abortions, and low body weight) associated with maternal toxicity (mortality) was observed at doses of 5 and 10 mg/kg/day. The no observed adverse effect doses of 600, 200 and 2 mg/kg/day in mice, rats and rabbits represent 9, 6, and 0.1 times, respectively, the maximum recommended human dose on a mg/m^2 basis. Calculations assume an oral dose of 320 mg/day and a 60-kg patient.

8.2 Lactation

(b) (4)

Data

In lactating rats, maximum milk levels of unchanged nebivolol were observed at 4 hours after single and repeat doses of 2.5 mg/kg/day. The daily dose (mg/kg body weight) ingested by a rat pup is 0.3% of the dam dose for unchanged nebivolol.

(b) (4)



PATIENT INFORMATION

WHO SHOULD NOT TAKE BYVALSON?

Do not take BYVALSON if you:

- [redacted] (b) (4)

WHAT SHOULD I TELL [redacted] (b) (4) BEFORE TAKING BYVALSON?



WHAT ARE POSSIBLE SIDE EFFECTS OF BYVALSON?

BYVALSON may cause [redacted] (b) (4) serious side effects:

- [redacted] (b) (4)
- [redacted]

Appendix B: Applicant's Review of Published Literature for Valsartan use during pregnancy

First Trimester Exposure to Valsartan: Case Reports

In Biswas (2002), a pharmacovigilance study performed by general practitioners in the United Kingdom reported four pregnancies in which the mother was treated with valsartan during the first trimester of pregnancy. One of these four patients underwent a therapeutic abortion because of maternal hypertension, and no fetal abnormalities were noted. Two pregnancies ended with first trimester miscarriages but no fetal abnormalities were documented. The fourth woman had a healthy, live-born child with no abnormalities.

In Chung (2001), 2 women were exposed to valsartan during a portion of their pregnancies, one for 7 weeks and the other for 10 weeks of the first trimester of their pregnancies. Both pregnancies proceeded to the delivery of live babies, with no congenital abnormalities or evidence of renal dysfunction.

Second and Third Trimester Exposure Valsartan: Case Reports

In Schaefer (2003), fetal malformations were observed in 2 (6%) of 32 infants born to women who were administered an angiotensin receptor blocker (ARB) during the first trimester of pregnancy; one of several ARBs were used by women in this report. An infant born to one of these mothers, treated with valsartan until the 13th week of pregnancy, had a cleft palate, patent ductus arteriosus, coarctation of the aorta, and growth retardation.

In Chung (2001), a mother was treated with valsartan until week 18 of gestation and gave birth to an apparently normal infant. This infant had growth retardation, which the authors attribute to the underlying maternal hypertension.

In Berkane (2004), a woman with chronic hypertension was treated with valsartan until gestation week 20, when complete anhydramnios was observed. Six days after interruption of the treatment, amniotic fluid reappeared. At week 38.5, an elective cesarean was performed due to the recent polomyomectomy. The baby did not show any abnormality: there were no dysmorphic features such as hypoplasia of the cranial bones or joint contractures. At six months, clinical follow-up of the baby did not show any problem.

In Briggs and Nagoette (2001), a woman with well-controlled chronic hypertension and diet- controlled type 2 diabetes mellitus was treated with valsartan and atenolol until pregnancy was diagnosed at 24 weeks gestation. An ultrasound examination revealed normal fetal growth and anatomy but anhydramnios. Valsartan was discontinued and amniotic fluid volume normalized within two weeks. Intrauterine fetal death was documented at 33 weeks gestation.

In Shimada (2015), a woman who had been treated with valsartan and amlodipine until week 24 of her pregnancy presented with anhydramnios during an ultrasound examination. Her medications were switched to nifedipine and amlodipine, leading to an increase in amniotic fluid. After the drug switch, her pregnancy course was unremarkable except for fetal growth restriction. After birth, the neonate appeared to be normal except for being

small for gestational age. Respiration and cranial ossification were normal. Ultrasound study of the kidneys was unremarkable.

In Martinovic (2001), a pregnant woman had been treated with valsartan and presented initially at 24 weeks gestation, at which time severe oligohydramnios was seen on ultrasonography. Termination of pregnancy was done at 27 weeks. In a second case, a mother who had been taking valsartan and hydrochlorothiazide for 4 years presented at 28 weeks gestation with complete absence of amniotic fluid. Two weeks after substitution of these drugs, amniotic fluid volume was normal, but there were fetal abnormalities, including renal hyperechogenicity, dilatation of cerebral ventricles, and narrow chest.

In Bos-Thompson (2005), a hypertensive woman treated with valsartan and hydrochlorothiazide became pregnant. At 28 weeks gestational age, severe anhydramnios associated with high β_2 -microglobulin levels in the fetal blood cord was observed. Upon discontinuation of valsartan, fetal renal prognosis improved. At the age of 2.5 years, the child presented with only mild chronic renal insufficiency. Growth parameters were within the normal range, and there was no evidence of developmental delay.

In Hunseler (2011), a woman received valsartan for 31 weeks during pregnancy. Ultrasound findings detected oligohydramnios and suspicion of polycystic kidneys. After birth, the child had impaired diuresis, enlarged kidneys, and required dialysis for 7 months. The child was diagnosed with renal insufficiency stage IV, sensorineural deafness, and ulnar deviation of hands with reduced muscular strength. In a second case, a woman received valsartan for 42 weeks during pregnancy. There were no prenatal ultrasound data available. At birth, the child has anuria with normal size kidneys. The child died at Day 2 due to cardiorespiratory failure.

In Schindera (2012), a woman was treated with valsartan during the entire pregnancy and presented at 35 weeks of gestation with preterm labor and complete anhydramnios. After spontaneous delivery the eutrophic male infant showed typical signs of -sartan fetotoxicity including neonatal anuria, enlarged hyperechogenic kidneys, initial arterial hypotension, limb contractures, skull bone hypoplasia and a narrow chest. During the first days of life arterial hypertension developed and persisted until last follow-up at 24 months. Antihypertensive therapy with amlodipine was necessary from 7 months of life until last follow-up.

In Vendemmia (2005), a woman was treated with valsartan and hydrochlorothiazide for 2 years. Ultrasonography was normal until 24 weeks of gestation. A subsequent ultrasound scan at 36 weeks showed oligohydramnios. After birth, echocardiography showed severe pulmonary artery hypertension. The patient needed mechanical ventilation, followed by high frequency oscillations, inhaled NO, exogenous surfactant administration and IV epoprostenol. Echography showed hyperechogenic kidneys with absent cortico-medullary differentiation. Limb deformations consisted of bilateral talus valgus and fixed internal rotation of the right hand. She had a Potter's syndrome facies, while the fontanelles were enlarged, the cranial sutures widely open, and skull bones were hypoplastic.

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/s/

MIRIAM C DINATALE
03/14/2016

LYNNE P YAO
03/16/2016

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: February 19, 2016

Requesting Office or Division: Division of Cardiovascular and Renal Products

Application Type and Number: NDA 206302

Product Name and Strength: Byvalson (Nebivolol and Valsartan) tablets (b) (4)

Submission Date: February 12, 2016

Applicant/Sponsor Name: Actavis Pharma, Inc.

OSE RCM #: 2015-2260-1

DMEPA Primary Reviewer: Sarah Thomas, PharmD

DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD

1 PURPOSE OF MEMO

The Division of Cardiovascular and Renal Products (DCRP) requested that we review the revised container labels and carton labeling for Byvalson submitted on February 12, 2016 (Appendix A) for the risk of medication error. The revisions are in response to our previous review of the labels and labeling for the proposed Byvalson (Nebivolol and Valsartan) (b) (4) tablets (See DARRTS Labeling Reviews dated October 22, 2014 and January 19, 2016).^{1,2}

¹ Jones G. Label and Labeling Review for Byvalson (NDA 206302). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 Oct 22. 13 p. OSE RCM No.: 2014-506.

² Thomas S. Label and Labeling Review for Byvalson (NDA 206302). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 Jan 19. 9 p. OSE RCM No.: 2015-2260.

2 CONCLUSION

Actavis Pharma, Inc. incorporated the majority of our recommendations from the previous reviews, with the exception of not relocating the lot number and expiration date from the bottom of the tray labeling to a side panel. Per Actavis Pharma, Inc., the lot number and expiration date on the bottom of the tray labeling cannot be moved to a side panel because the portion including these numbers is a cut-out so that the bottom of the carton is visible. Per Actavis Pharma, Inc., this cannot be moved due to the production line.

We find the revised labels and labeling acceptable from a medication error perspective. We note the redundant word “tablet” after the strength statement, and an inconsistent labeler code (first segment of NDC number) on the revised sleeve labeling; thus we point out to bring to Actavis Pharma, Inc.’s attention.

3 RECOMMENDATIONS FOR ACTAVIS PHARMA, INC.

We recommend the following be implemented prior to approval of this NDA:

A. General Comments

1. Consider removing the word “tablets” from the strength statement inside the green highlight so that the strength statement reads [REDACTED] (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 [REDACTED] (b) (4) whereas it’s “61874” on all other container labels and carton labeling.

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/s/

SARAH E THOMAS
02/19/2016

CHI-MING TU
02/22/2016

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: January 19, 2016
Requesting Office or Division: Division of Cardiovascular and Renal Products
Application Type and Number: NDA 206302
Product Name and Strength: Byvalson (Nebivolol and Valsartan) tablets (b) (4)
Submission Date: September 29, 2015
Applicant/Sponsor Name: Actavis Pharma, Inc.
OSE RCM #: 2015-2260
DMEPA Primary Reviewer: Sarah Thomas, PharmD
DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD

1 PURPOSE OF MEMO

The Division of Cardiovascular and Renal Products (DCRP) requested that we review the revised container labels, carton labeling, prescribing information, and patient information for Byvalson (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹ Of note, the Applicant is now only seeking approval of the (b) (4) mg strength of Byvalson.

¹ Jones G. Label and Labeling Review for Byvalson (NDA 206302). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 Oct 22. 13 p. OSE RCM No.: 2014-506.

2 CONCLUSION

The revised container labels, carton labeling, and prescribing information for Byvalson are unacceptable from a medication error perspective. While Actavis Pharma, Inc. incorporated our recommendations from the previous review¹, changes in proposed product characteristics and the mock up samples of the revised container labels and carton labeling led DMEPA to identify additional areas for improvement. Therefore, we provide recommendations in Section 3 to Actavis Pharma, Inc. and DCRP for improvement of the revised container labels, carton labeling, and prescribing information. The patient information is acceptable from a medication safety perspective, and we have no recommendations for improvement.

3 RECOMMENDATIONS FOR THE DIVISION

A. General Recommendations for Prescribing Information (PI)

1. Add the unit of measurement immediately following the numbers that designate the strength throughout the PI. For example, revise the strength (b) (4) to read (b) (4)

B. Section 2, Dosage and Administration

1. We recommend providing the dosing range and specifying the maximum safe and efficacious dose for Byvalson.
2. In section 2.3, we recommend specifying (b) (4)

C. Section 16, How Supplied/Storage and Handling

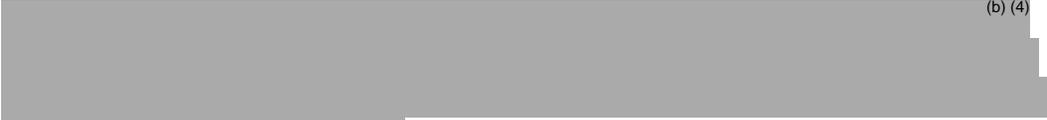
1. We recommend clarifying (b) (4) which is suggested in Section 16 with the following statement: (b) (4)
(b) (4), we recommend removing this detail from the aforementioned statement and all container labels.

4 RECOMMENDATIONS FOR ACTAVIS PHARMA, INC.

We recommend the following be implemented prior to approval of this NDA:

A. General Recommendations for Container Labels and Carton Labeling:

1. Since only a single strength of Byvalson is under development now, and the only proposed recommended dose is one tablet taken orally once daily, revise the usual dosage statement to read "Usual dose: Take one tablet by mouth once daily." Alternatively, if the proposed product has a dose range, then revise the usual dosage statement to read "Usual dose: See Prescribing Information."

2. 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)
Revise all container labels so this statement is presented, or providing justification for the inconsistency.
- 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. 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 the digits in the NDC number present 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 the digits 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.

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/s/

SARAH E THOMAS
01/19/2016

LUBNA A MERCHANT on behalf of CHI-MING TU
01/19/2016

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: October 21, 2014

TO: Norman Stockbridge, M.D.
Director,
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Office of New Drugs

FROM: Hasan A. Irier, Ph.D.
Pharmacologist,
Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Sam H. Haidar, R.Ph., Ph.D.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

William H. Taylor, Ph.D.
Director,
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIR Covering NDA 206-302,
Nebivolvol/Valsartan Fixed Dose Combination, sponsored
by Forest Research Institute, Inc., NJ

At the request of the Division of Cardiovascular and Renal Products, Office of Drug Evaluation I, the Division of Bioequivalence and GLP Compliance (DBGLPC) conducted inspections of the clinical and analytical portions of the following bioequivalence study:

Study Number: NAC-PK-07

Study Title: " A single-center, randomized, open-label, two-way crossover, single-dose study to evaluate the bioequivalence of the current fixed-dose combination formulation of nebivolol and valsartan and the new fixed-dose combination

formulation of nebivolol and valsartan in healthy subjects"

ORA investigator Brunilda Torres (Florida District Office) audited records of the clinical portion of the study during the FDA inspection conducted at Clinical Pharmacology of Miami, Inc., in Miami, Florida, from October 6 to 9, 2014. Reserve samples of test and reference were collected according to the FDA regulation.

ORA investigator (b) (4) ((b) (4) District Office) accompanied by DBGLPC scientists Drs. Young Moon Choi and Hasan A. Irier audited the analytical portion of the study during the FDA inspection (b) (4)

The audits included a thorough review of study records, examination of facilities, equipment, interviews and discussions with the firm's management and staff. At the conclusion of the clinical and analytical site inspections, no objectionable conditions were observed at either sites and Form FDA-483 was not issued.

Conclusion:

Following review of the inspectional findings, this DBGLPC reviewer conclude that the clinical and bioanalytical data of study NAC-PK-07 are acceptable for further Agency review.

Hasan A. Irier, Ph.D.
Pharmacologist
Bioequivalence Branch, DBGLPC, OSI

Final Classifications:

NAI: Clinical Pharmacology of Miami, Inc., Miami, FL
(FEI#: 3010800672)

NAI: (b) (4)
(FEI#: (b) (4))

Page 3 -NDA 206-302, Nebivolol/Valsartan Fixed Dose Combination sponsored by Forest Research Institute Inc., NJ

CC:

OSI/DBGLPC/Taylor

/Haidar/Bonapace/Choi/Skelly/Dasgupta/Irier

OSI/DBGLPC/PM/Dejernett/Johnson/Nkah/Fenty-Stewart

CDER/OND/ODEI/DCRP/PM/Montealeone/Mahayni

ORA/ (b) (4) -DO/ (b) (4) /

ORA/FLA-DO/Sinninger/Torres/

Draft: HAI 10/09/2014

Edits: JBP 10/15/2014

OSI: File BE6705; O:\BE\EIRCOVER\206302.for.nebval.doc

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good

Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical

sites/ Clinical Pharmacology of Miami, Inc., in Miami,

Florida/Analytical sites/ (b) (4)

(b) (4)

FACTS: 8768889

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/s/

HASAN A IRIER
10/21/2014

SAM H HAIDAR
10/22/2014

WILLIAM H TAYLOR
10/22/2014

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: October 22, 2014

Requesting Office or Division: Division of Cardiovascular and Renal Products

Application Type and Number: NDA 206302

Product Name and Strength: Byvalson (Nebivolol/Valsartan) Tablets
5 mg/80 mg, 5 mg/160 mg, 10 mg/160 mg, 10 mg/320mg,
and 20 mg/320 mg

Product Type: Multi-ingredient Product

Rx or OTC: Rx

Applicant/Sponsor Name: Forest Laboratories, Inc.

Submission Date: July 3, 2014

OSE RCM #: 2014-506

DMEPA Primary Reviewer: Grace P. Jones, PharmD, BCPS

DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

This review evaluates the proposed Byvalson (Nebivolol/Valsartan) Prescribing Information (PI), container labels and carton labeling for areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B (N/A)
Previous DMEPA Reviews	C (N/A)
Human Factors Study	D (N/A)
ISMP Newsletters	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Byvalson is a multi-ingredient product that contains the two currently marketed products, nebivolol (Bystolic) and valsartan (Diovan). Hence, we compared the current marketed label and labeling of Bystolic¹ to the proposed labels and labeling for Byvalson since both formulations are likely to be stored in close proximity on pharmacy shelves, as both proprietary names begin with the letters “By.” The Applicant uses (b) (4)

(b) (4)

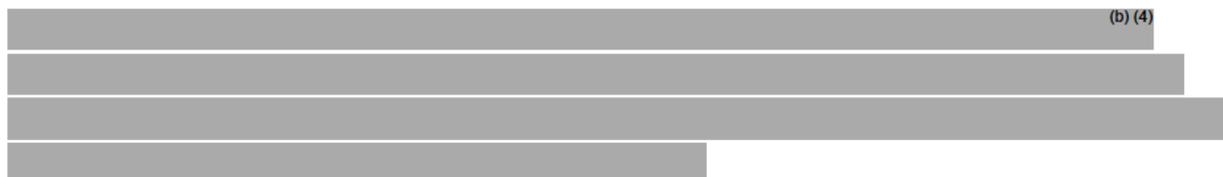
Our review found (b) (4)

(b) (4)

(See Figure 1 for Bystolic container label images, and Appendix G for Byvalson container labels and carton labeling).

¹ Bystolic container labels. <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=8b8ad213-1dc8-454e-a524-075685c0e1a8>

Figure 1. Bystolic Container Label (NDA 021742 Annual Report-6, submitted 2/13/2014)



4 CONCLUSION & RECOMMENDATIONS

We determined the proposed container label, carton labeling, and Prescribing Information for Byvalson could be improved to increase the prominence and readability of important information to promote safe use of the product.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information (PI)

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

4.2 RECOMMENDATIONS FOR FOREST LABORATORIES, INC.

- A. Container Labels and Carton labeling – including Container Label; Professional Sample Container, Carton, Tray Labeling; Professional Sample Container, Carton, Tray Labeling (Early Sample) (b) (4)
1. Revise the presentation of the established name so it is printed in letters that are at least half as large as the letters comprising the proprietary name. The established name should have a prominence commensurate with the prominence with such proprietary name, taking into account typography, layout, contrast and other printing features in accordance with 21 CFR 201.10(g)(2).
 2. Revise the strength expression to include the unit of measurement immediately following all numbers on the principal display panel and the side panel. For example, revise the statement (b) (4)
 3. Revise the color scheme for the 5 mg/80 mg strength of Byvalson to improve readability and provide sufficient color contrast between the two colors. The currently proposed color scheme of white text on (b) (4) highlight compromises readability (b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)
 4. Relocate the net quantity statement to the bottom of the principal display panel (PDP) (b) (4) and away from the strength statement for all applicable container labels and carton labeling (b) (4)
(b) (4)
 5. (b) (4)
(b) (4)
(b) (4)
(b) (4)

² Guidance for Industry (draft): Safety considerations for container labels and carton labeling design to minimize medication errors

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf>

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Byvalson that Forest Laboratories, Inc. submitted on July 3, 2014.

Table 2. Relevant Product Information for Byvalson	
Initial Approval Date	N/A
Active Ingredient	nebivolol and valsartan
Indication	treatment of hypertension
Route of Administration	oral
Dosage Form	tablet
Strength	5 mg/80 mg, 5 mg/160 mg, 10 mg/160 mg, 10 mg/320 mg, 20 mg/320 mg
Dose and Frequency	one tablet daily (b) (4)
How Supplied	30 and 90 count bottles; (b) (4) 7 count sample
Storage	20°C to 25°C (68°F to 77°F)

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L:Drive on September 19, 2014 using the terms, Byvalson, to identify our previously completed reviews.

C.2 Results

A proprietary name review was completed on August 12, 2014 for Byvalson under the same NDA 206302 (OSE RCM# 2014-25586). The information in this review was not relevant to the Byvalson labels and labeling evaluation.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis³, along with postmarket medication error data, we reviewed the following Byvalson labels and labeling submitted by Forest Laboratories Inc. on July 3, 2014.

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

(b) (4)

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

³ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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

/s/

GRACE JONES
10/22/2014

CHI-MING TU
10/22/2014

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: September 4, 2014

TO: Raj Madabushi, Team Leader
Shen Xiao, Medical Officer Clinical
Michael Monteleone, Regulatory Health Project Manager
Division of Cardio-Renal Drug Products

FROM: Sharon K. Gershon, Pharm. D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 206302

APPLICANT: Forest Laboratories, Inc.

DRUG: nebivolol and valsartan fixed dose combination (FDC)

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority

INDICATION: Treatment of hypertension

PROTOCOL: 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 (FDC) in Patients with Stage 1 or Stage 2 Essential Hypertension

CONSULTATION REQUEST DATE:	April 15, 2014
INSPECTION SUMMARY GOAL DATE:	November 8, 2014
ADVISORY COMMITTEE	September 9, 2014
DIVISION ACTION GOAL DATE:	November 21, 2014
PDUFA DATE:	December 24, 2014

I. BACKGROUND:

Forest Laboratories, Inc. submitted NDA 206302, for neбиволол and valsартан in a fixed-dose combination product, compared with the monotherapy components and placebo, in patients with stage 1 or stage 2 essential hypertension. Nebivolol a beta-blocker (β -blocker) and valsartan, an angiotensin II receptor blocker (ARB) are both approved in the U.S. as monotherapy or in combination with other antihypertensive agents for the treatment of hypertension. The β -blocking and the vasodilator effects of neбиволол combined with the blockade of the renin-angiotensin system by an ARB, such as valsartan, are proposed to provide better blood pressure control than the component monotherapies alone.

The Applicant provided data from Study NAC-MD-01, a Phase III study, which they believe provide sufficient evidence for the efficacy of neбиволол and valsартан fixed-dose combination (FDC), indicated for patients with hypertension. The study design consisted of one week of screening, followed by a single-blind placebo washout/run-in period of up to six weeks, followed by an eight-week double-blind treatment period, followed by a one-week down-titration period. Patients were randomized in a 2:2:2:2:2:2:1 ratio to neбиволол and valsартан (5/80, 5/160, 10/160 mg), neбиволол monotherapy (5, 20 mg), valsартан monotherapy (80, 160 mg), or placebo. The dose was doubled after four weeks. At the end of eight weeks of double-blind treatment, a one-week double-blind down-titration period followed. The primary efficacy endpoint was the change in sitting trough diastolic blood pressure (DBP) from baseline to Week 8 as measured by an Omron blood pressure monitoring device

This was a multicenter study of approximately randomized 4161 subjects with 550 per active treatment arm and 270 in placebo arm, at approximately 460 study centers in the United States.

Rationale for Site Selection:

The sites chosen for inspection had the following characteristics: Dr. DiGregorio had very high enrollment (103), and high treatment effect size in the FDC treatment arm. Dr. Lara had relatively high enrollment (69), and high treatment effect size in the FDC treatment arm. Dr. Ledesma had very high enrollment (103) and a sponsor complaint issued in 2009 in which his site was terminated due to GCP noncompliance for a different application. Dr. Ledesma was last inspected in January 2011; that inspection was classified VAI for inadequate and inaccurate records.

II. Results

Name of CI/Address	Protocol # and # of Subjects	Inspection Dates	Final Classification
Michael DiGregorio 1440 N. Eastern Ave Las Vegas, NV 89101	NAC-MD-01 Site 1011 103 subjects	August 1 – 15, 2014	VAI
Miriam Lara 6850 Coral Way, Suite 409 Miami, FL 33155	NAC-MD-01 Site 1154 69 subjects	June 16 – 19, 2014	VAI
Gilbert Ledesma 707 N. Fielder Rd, Suite A Arlington, TX 76012	NAC-MD-01 Site 1094 103 subjects	June 5 – 19, 2014	NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. Michael DiGregorio (Site 1011)

1440 N. Eastern Ave
Las Vegas, NV 89101

a. What was inspected: This inspection was conducted according to Compliance Program 7348.811. Dr. DiGregorio has thirteen IND studies in the CDER clinical investigator database and no prior inspections. At this site, 187 subjects were screened, 90 subjects enrolled, and 84 subjects completed the study. The FDA field investigator reviewed records for thirty subjects during the inspection. The review included source documents, progress notes, eligibility criteria requirements, concomitant medications, signed informed consent document (ICD), laboratory results, reported adverse events, subject's follow-up visits, subject diaries, IRB and sponsor correspondences, drug accountability records, protocol deviations, and other general study documentation.

b. General observations/commentary: Dr. DiGregorio oversaw the conduct of the study including recruiting patients; reviewing inclusion/inclusion criteria; obtaining informed consent, medical history, and vital signs; performing physical examinations; obtaining and preparing lab samples; instructing subjects on study procedures; interviewing patients about adverse events (AEs) and concomitant medications; evaluating AEs/SAEs, completing SAE forms and submitting to the sponsor; dispensing/collecting study drug; performing drug accountability, making entries/corrections on CRFs/e-CRFs; maintaining the regulatory binder; signing protocol contact form; obtaining ECG; and collecting/reviewing patient diaries.

The sponsor's clinical study monitor performed a site initiation visit on February 7, 2012; interim monitoring visits occurred between March 6, 2012 and May 1, 2013. A close-out visit occurred May 16 – 17, 2013. Data queries were filed in the subject's binder. Data corrections were reported utilizing the Data Correction Forms (DCF), and maintained with the CRFs.

There was no evidence of under-reporting of adverse events and the primary efficacy endpoint data were verifiable.

At the end of the inspection, a one observational Form FDA 483 was issued for an **investigation not conducted according to the signed statement of investigator**. The cited deviations (listed below) were observed during review of 30 subjects' clinical study records, and were not included in the sponsor's data listings. Dr. DiGregorio acknowledged the observations during the inspection, and promised a response in writing. Specifically,

- i. The protocol required performance: of vital signs measurements at Visits 1 to 15; clinical laboratory determinations at Visit 1 to include hematology, chemistry, and urinalysis; urine pregnancy test (female subjects) at Visits 1, 9, and 14; urine drug screening (UDS) at Visits 1 and 9, and ECG testing at Visits 1, 9, 14, & 15. The protocol also required that the UDS and urine pregnancy tests be completed at the study center before randomization; and samples would be sent to the central laboratory for confirmation. The FDA field investigator found

- a. In several instances the subjects' UDS was not performed at the study center before being randomized into the clinical study. Examples included Subjects 001, 003, 004, 005, and 006 who were randomized into the study based on the central laboratory's negative test results.
 - b. In several occurrences, serum pregnancy tests were not performed by the central laboratory before subjects' were randomized into the clinical the study. Examples included Subjects 143, 154, 170, and 176.
 - c. In several instances, vital sign measurements were not performed on the day of subjects' randomization. Examples included Subjects 006, 091, and 154.
 - d. Clinical laboratory assessment for hematology was not performed by the central laboratory for Subject 079 during Visit 1 (Screening) and the subject was randomized into the study.
 - e. Serum pregnancy test was not performed for Subject 117 during Visit 14 (End of Double Blind Treatment).
- ii. The protocol required that at Visit 11 (Dose Escalation) subjects be evaluated to determine whether they were eligible to continue. Further, the protocol required administering double-blind Investigational Product (IP) from the collected blister card (Visit 10) upon completion of all pre-dose procedures, and subjects would be dispensed and begin taking the up-titrated dose at the end of Visit 11 on the next day. In several instances, subjects were administered study drug on the same day of Visit 11 instead of the next day. Examples include Subjects 014, 017, 111, 116, 123, and 127.
 - iii. The protocol required that at Visit 15 (End of Study) a 12-lead ECG be conducted, and subjects who had abnormal QTcF results (>450 msec for females) will undergo ECG assessment until the abnormal value falls within range or is judged upon reassessment to be clinically significant or unlikely to change. The FDA field investigator observed that on July 13, 2012 (Visit 15), Subject 019 has QTcF value of 470 msec. No further follow-up visit was conducted to reassess this subject's ECG.

c. Assessment of data integrity: Although regulatory violations were noted above, it is unlikely based on the nature of the violations that they significantly affect overall reliability of safety and efficacy data. The data derived from Dr. DiGregorio's site is considered acceptable.

Note: The final EIR for Dr. DiGregorio was not available at the time this clinical inspection summary was written. The observations noted are based on preliminary EIRs or email communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

2. Dr. Miriam Lara (Site 1154)

6850 Coral Way, Suite 409
Miami, FL 33155

a. What was inspected: This inspection was conducted according to Compliance Program 7348.811. Dr. Lara has five IND studies in the CDER clinical investigator database and no prior inspections. Dr. Lara had relatively high enrollment (69 subjects), and high treatment effect size.

At this site, 101 subjects were screened; sixty-nine subjects randomized and sixty-seven subjects completed the study. Subject 01045 was terminated early after the site received notice from the sponsor confirming the subject had enrolled at another site under the same protocol. Subject 01064 withdrew consent and was discontinued from the study.

The following records were audited: signed informed consent documents for sixty-nine subjects; source documentation for thirty-one subjects; correspondences from the sponsor and IRB; adverse event reports for all enrolled subjects; protocol deviation forms; and study drug accountability records.

b. General observations/commentary: No serious adverse events were experienced for any subject during the study. No data discrepancies between data listings and source documents were noted for any subject. Study data appeared as legible and organized. Printouts of blood pressure measurements associated with the primary efficacy endpoints were present in the subject's source documents, and were verifiable. At the conclusion of the inspection a two observational FDA-483 was issued for:

1) Failure to conduct the study according to the signed investigator statement and the investigational plan [21 CFR 312.60];

Specifically, the field investigator identified three subjects who did not meet all protocol inclusion and exclusion criteria and were randomized into the study. These protocol violations were reported to the sponsor (included in the data listings) but were not reported to the IRB.

- Subject 01003 had a history of gastric bypass and was randomized (exclusion criteria #19)
- Subject 01068 had right bundle branch on ECG at screening and was randomized (exclusion criteria #7).
- Subject 01007 had out of range QTcF value of 430 msec and was randomized (exclusion criteria #5).

2) Failure to report promptly to the IRB all unanticipated problems involving risk to human subjects [21 CFR Part 56].

Specifically, the above three violations were not reported to the IRB.

Dr. Lara's response letter to the FDA dated July 7, 2014, promised corrective action to the observations. Her response is considered acceptable.

c. Assessment of data integrity: Although a few regulatory violations were observed during the inspection, it is unlikely based on the nature of the violations that they significantly affect overall reliability of safety and efficacy data. In general, the study was conducted well at this site, and OSI recommends the data as acceptable in support of the claimed indication.

3. Gilbert Ledesma (Site 1094)

707 N. Fielder Rd, Suite A
Arlington, TX 76012

a. What was inspected: Dr. Ledesma has 25 IND studies in CDER's Clinical Investigator database. A prior inspection at this site was conducted in January 2011 and classified as VAI for 1) failure to promptly report to the IRB all unanticipated problems involving risk to human subjects; and 2) failure to maintain adequate and accurate records with respect to data pertinent to the investigation. For the current NDA, Dr. Ledesma was inspected because of large enrollment and a sponsor complaint that was issued for a different application in 2009 for which his site was terminated from that study for GCP noncompliance.

This site screened 211 subjects and enrolled 103 subjects. A total of 97 subjects completed the study, and six subjects terminated early. There were no deaths. The field investigator reviewed thirty percent of subject records for inclusion and exclusion criteria, subject randomization, blood pressure measurements, adverse events, concomitant medications, laboratory reports, and test article accountability records. The field investigator was given access to the patient's paper medical charts, electronic medical charts, and the electronic data capture CRF's.

The field investigator also reviewed regulatory binders that included the study protocols, delegation logs, sponsor correspondences, IRB approvals, protocol deviation logs, all adverse events, including SAEs, and informed consent forms.

The sponsor Forest Laboratories provided monitoring during the study. On-site monitoring occurred every month.

b. General observations/commentary: Observations were made concerning a subject not signing the correct version of the informed consent document (ICD). This item was discussed with Dr. Ledesma during the inspection. For example, Subject 100 signed ICD Version 3 on June 29, 2012 even though the IRB approved ICD Version 3.1 on June 26, 2012. The subject was re-consented using Version 3.1 on July 6, 2012. The above protocol deviations were not submitted to the sponsor. This issue was identified for one other subject, and is unlikely to significantly impact the quality of the data at this site.

Another observation was discussed concerning blood pressure measurements. For two instances, the PI used a manual calculation of the average of three measurements instead of using the average of four BP readings that were taken. For example, for Subject 14, there were four blood pressure measurements made on April 4, 2012, and the average calculated BP value was 161/96. The PI used only three BP measurements and manually calculated the BP average as 160/96. The manual calculated average was entered into the CRF and appeared in the data listings. This observation is unlikely to significantly impact data integrity.

c. Assessment of data integrity: No Form FDA 483 was issued at the close of the inspection, although there were several discussion items. These are unlikely to affect the efficacy or safety outcomes of the study. The study was conducted well at this site, and OSI recommends that the data is acceptable in support of the claimed indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Three domestic clinical investigator inspections were conducted in support of NDA 206302. Minor regulatory violations were found during the inspections of Dr. DiGregorio (Site 1011) and Dr. Lara (Site 1154) for failure to follow the investigational plan, but these are unlikely to significantly impact the integrity of the data submitted in support of this NDA. No regulatory violations were found during the inspection of Dr. Ledesma (Site 1094), and the inspection was classified NAI. Although regulatory violations were noted at Site 1011 and Site 1154, they are unlikely to significantly impact the primary efficacy or safety analysis for this study. Therefore, the data from this study may be considered reliable.

Note: The final EIR for Site 1011 (Michael DiGregorio) was not available at the time this clinical inspection summary was written. The observations noted are based on preliminary EIRs or email communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

{See appended electronic signature page}

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

/s/

SHARON K GERSHON
09/05/2014

SUSAN D THOMPSON
09/05/2014

KASSA AYALEW
09/05/2014

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 206302 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: (b) (4) Established/Proper Name: Nebivolol/Valsartan Dosage Form: tablet Strengths: 5/80mg; 5/160mg; 10/160mg; 10/320mg; 20/320mg		
Applicant: Forest Laboratories Agent for Applicant (if applicable):		
Date of Application: February 23, 2014 Date of Receipt: February 24, 2014 Date clock started after UN:		
PDUFA Goal Date: December 24, 2014		Action Goal Date (if different):
Filing Date: April 25, 2014		Date of Filing Meeting: April 3, 2014
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): treatment of hypertension		
Type of Original NDA: AND (if applicable)	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)	
Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.</i>		
Type of BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)	
<i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s):				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, explain in comment column.</i>			x	
<i>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</i>	<input type="checkbox"/>	<input type="checkbox"/>	x	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>	<p><input type="checkbox"/></p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>	<p><input type="checkbox"/></p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>	<p><input type="checkbox"/></p>																	
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1482 1349 1619"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration													<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>	<p><input type="checkbox"/></p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>																		

Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: 3 <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
For BLAs: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Format and Content	
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?	

<p>included with authorized signature per 21 CFR 54.4(a)(1) and (3)?</p> <p><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>				
Clinical Trials Database	YES	NO	NA	Comment
<p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<u>Proprietary Name</u>	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<u>REMS</u>	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<u>Prescription Labeling</u>	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide)			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input checked="" type="checkbox"/> Carton labels			
	<input checked="" type="checkbox"/> Immediate container labels			
	<input type="checkbox"/> Diluent			
	<input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send <i>WORD</i> version if available)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label			
	<input type="checkbox"/> Immediate container label			
	<input type="checkbox"/> (b) (4)			
	<input type="checkbox"/> Consumer Information Leaflet (CIL)			
	<input type="checkbox"/> Physician sample			
	<input type="checkbox"/> Consumer sample			
	<input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?	<input type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): May 21, 2013 (CMC) September 5, 2013 (Clinical) – written comments only, no meeting	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 3, 2014

BLA/NDA/Supp #: 206302

PROPRIETARY NAME: (b) (4)

ESTABLISHED/PROPER NAME: nebivolol/valsartan

DOSAGE FORM/STRENGTH: tablet 5/80mg, 5/160mg, 10/160mg, 10/320mg, 20/320mg

APPLICANT: Forest Laboratories

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): treatment of hypertension

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Michael Monteleone	Y
	CPMS/TL:		
Cross-Discipline Team Leader (CDTL)	Rajanikanth Madabushi		Y
Clinical	Reviewer:	Shen Xiao	Y
	TL:	Aliza Thompson	N

Clinical Pharmacology	Reviewer:	Bilal AbuAsal	Y
	TL:		
Biostatistics	Reviewer:	George Kordzakhia	Y
	TL:	Peiling Yang	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Philip Gatti	Y
	TL:	Thomas Papoian	N
Product Quality (CMC)	Reviewer:	Rao Kambhampati	Y
	TL:	Kasturi Srinivasachar	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Erika Pfeiler	N
	TL:		
Facility Review/Inspection	Reviewer:	Vibhakar Shah	N
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Jean Olumba	Y
	TL:	Lisa Khosla	N
OSE/DRISK (REMS)	Reviewer:		
	TL:	Kim Lehrfeld	N

Other reviewers	Houda Mahayni, Biopharmaceutics	Y
Other attendees	Tamra Meyer, DEP2	

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> 505(b)(2) filing issues: <ul style="list-style-type: none"> Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<p><input type="checkbox"/> Not Applicable</p> <p>BE study, NAC-PK-05</p>
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <p>If no, explain:</p>	
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<p><input type="checkbox"/> Not Applicable</p>
<p>CLINICAL</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input checked="" type="checkbox"/> Review issues for 74-day letter</p>
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <p>If no, explain:</p>	
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <input checked="" type="checkbox"/> YES <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> 	<p>Date if known: September 9, 2014</p> <p><input type="checkbox"/> NO</p> <p><input type="checkbox"/> To be determined</p> <p>Reason: Discuss effect size</p>

<ul style="list-style-type: none"> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p style="margin-left: 40px;">If no, was a complete EA submitted?</p> <p style="margin-left: 40px;">If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application’s pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<p><input checked="" type="checkbox"/> N/A</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Division</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V):</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p>	

Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
<input type="checkbox"/>	Other

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

/s/

MICHAEL V MONTELEONE
05/09/2014

OSI Consult Request for Biopharmaceutical Inspections	
Date	April 15, 2014
Subject	Request for Biopharmaceutical Inspections (BE)
Addressed to	William H. Taylor, PhD Director, Division of BE and GLP Compliance Office of Scientific Investigations william.taylor1@fda.hhs.gov
Consulting Office/Division	Division of Cardiovascular and Renal Products
Project Manager	Michael Monteleone
Application Type	PEPFAR? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
	<input checked="" type="checkbox"/> NDA <input type="checkbox"/> BLA <input type="checkbox"/> ANDA
Application Number	206302
Drug Product	Nebivolol/Valsartan Fixed Dose Combination
Sponsor Name	Forest Research Institute, Inc.
Sponsor Address	Harborside Financial Center, Plaza V Jersey City, NJ 07311
US Agent (if applicable)	
US Agent Address	
Electronic Submission	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
PDUFA/BsUFA Due Date	12/24/2014
Action Goal Date	
OSI Review Requested By	Houda Mahayni, Biopharmaceutics Reviewer

Inspection Request Detail (All fields should be fill out completely)	
Study #1	
Study Number	NAC-PK-07
Study Title	A Single-Center, Randomized, Open-Label, 2-Way Crossover, Single-Dose Study to Evaluate the Bioequivalence of the Current Fixed-Dose Combination Formulation of Nebivolol and Valsartan and the New Fixed-Dose Combination Formulation of Nebivolol and Valsartan in Healthy Subjects
Study Type	<input checked="" type="checkbox"/> In vivo BE <input type="checkbox"/> In vitro BE <input type="checkbox"/> Permeability <input type="checkbox"/> Others (specify)
<input checked="" type="checkbox"/> Inspection Request - Clinical Site	<input checked="" type="checkbox"/> Inspection Request - Analytical Site
Facility #1 Name: Clinical Pharmacology of Miami, Inc. Address: 550 West 84th Street, Miami, FL 33014 (Tel) (Fax)	Facility #1 Name: High Standard Products/ Address: (Tel) (Fax)
Clinical Investigator: Ernesto Fuentes, M.D. (email)	Principal Analytical Investigator: (email)

<i>(please include specific review concerns or items to be addressed during the inspection in the appendix below)</i>	
<input checked="" type="checkbox"/> Study Report: (5.3.1.2) NAC-PK-07	<input checked="" type="checkbox"/> Validation Report: (5.3.1.2) PRD-RPT-BDM-00573 (Nebivolol) PRD-RPT-BDM-00575 (Valsartan) <input checked="" type="checkbox"/> Bioanalytical Report: (5.3.1.2) PRD-RPT-BDM-00615 (Nebivolol) PRD-RPT-BDM-00616 (Valsartan)

Study #2				
Study Number				
Study Title				
Study Type	<input type="checkbox"/> In vivo BE	<input type="checkbox"/> In vitro BE	<input type="checkbox"/> Permeability	<input type="checkbox"/> Others (specify)
<input type="checkbox"/> Inspection Request - Clinical Site	<input type="checkbox"/> Inspection Request - Analytical Site			
Facility Name: (or indicate if same as above) Address: (Tel) (Fax)	Facility Name: (or indicate if same as above) Address: (Tel) (Fax)			
Clinical Investigator: (email)	Principal Analytical Investigator: (email)			
Check one: <input type="checkbox"/> Routine inspection <input type="checkbox"/> For cause	Check one: <input type="checkbox"/> Routine inspection <input type="checkbox"/> For cause			
<i>(please include specific review concerns or items to be addressed during the inspection in the appendix below) Nothing specific</i>				
<input type="checkbox"/> Study Report:	<input type="checkbox"/> Validation Report: <input type="checkbox"/> Bioanalytical Report:			

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, OSI.

I. Appendix

Specific Items To be Addressed During the Inspection
<p>This request is for routine audits of the analytical and clinical sites for BE study NAC-PK-07. There are no items to be specifically addressed during the audit of these sites.</p>

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

/s/

MICHAEL V MONTELEONE
04/28/2014

HOUDA MAHAYNI
04/28/2014