

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206302Orig1s000

OTHER ACTION LETTERS



NDA 206302

COMPLETE RESPONSE

Forrest Laboratories, Inc.
Attention: Kathleen Waldron, MBA
Senior Director, Regulatory Affairs
Harborside Financial Center
Plaza V, Suite 1900
Jersey City, NJ 07311

Dear Ms. Waldron:

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

We acknowledge receipt of your amendments dated February 26, May 6, 15, 16, June 11, 12, 17, 19, 23, 25, July 2, 3, 25, August 6, 8, 12 (2), 27, 28, October 3, November 7 and 20, 2014.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

Based upon the principle that, absent a safety advantage, all components of a combination product ought to contribute meaningfully to the antihypertensive effect achievable with the individual agents (or to combinations of fewer agents), we concluded that Byvalson's effect was too small and a safety advantage had not been demonstrated. We explored with you the possibility that there were more responders than one might have expected on the basis of the observed mean treatment effect, but we concluded there was no evidence for such a population with exaggerated effect.

It is possible, of course, for you to develop a more compelling case for improvement in safety or tolerability of Byvalson compared with high dose nebivolol, and if you choose to explore this, we will gladly discuss protocol design with you.

However, you may find it worthwhile to pursue another possibility. We recognize that many physicians practice and guidelines promote use of lower-dose combination antihypertensive therapy on the basis that half or more of the treatment effect is manifest at the low dose, and, where the mechanisms are sufficiently distinct, one ought to expect more-or-less additive effects on blood pressure and avoidance of dose-related adverse reactions of either drug. We have not to date based an approval on such a principle, but we are willing to consider one, even absent

demonstration of better tolerability. We recommend that you abstract from your development program with Byvalson a characterization of the effects of the combination compared with effects of the corresponding components at the same dose and compare your results with similar information on approved combination antihypertensives, to the extent such data are available to you in drug labels or the literature. Your goal would be to show that Byvalson doses are about as additive as are other combinations one might expect to be more mechanistically independent. If you choose to explore this, since we have never based a decision on this principle, it will be important to discuss the data gathering and the preliminary results before you resubmit.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(1)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

CARTON AND CONTAINER LABELING

In your response, please submit draft carton and container labeling revised as follows:

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)

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)

5. (b) (4)

PROPRIETARY NAME

Please refer to correspondence dated, August 22, 2014 which addresses the proposed proprietary name, Byvalson. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.

¹ 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>

- Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
 4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
 5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
 6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
 7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
 8. Provide English translations of current approved foreign labeling not previously submitted.

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues:

Chemistry:

For the comparability protocol in section 3.2.R to change drug substance manufacturing sites, the data set, test methods, and acceptance criteria appears appropriate. When you resubmit your NDA, include your proposal to change or add drug substance manufacturers, including the name and address of any new site. Be advised that supplements are filed as a CBE-30 only if the proposed site is cGMP compliant for the intended operation at the time of submission. Please refer to the 'Guidance for Industry: Changes to an Approved NDA or ANDA,' section VI, for further information regarding filing categories for manufacturing facility change supplements.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully

address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

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

Sincerely,

{See appended electronic signature page}

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

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

/s/

NORMAN L STOCKBRIDGE
12/24/2014