CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205029Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205029

COMPLETE RESPONSE

Belcher Pharmaceuticals, LLC
Attention: Mihir Taneja
Vice President
6911 Bryan Dairy Road
Suite 210
Largo, FL 33777

Dear Mr. Taneja:

Please refer to your New Drug Application (NDA) dated November 30, 2012, received December 4, 2012, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for epinephrine injection 1 mg/mL.

We acknowledge receipt of your amendments dated January 3, 4, 8, February 6, March 4, 8, and April 8, 2013.

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.

PRODUCT QUALITY

1. In response to our question about evaluation of the manufacturing process for (b) (4) of *l*-epinephrine, you have stated that analysis of two batches of Epinephrine Injection (1 mg/mL) manufactured with (b) (4) You have also proposed a limit of (b) (4) in the drug product without providing adequate justification. However, you have not provided (b) (4) data from the two batches manufactured in February 2013 to support your contention.

   Therefore, we recommend that you re-evaluate the manufacturing process establishing the (b) (4) and provide data including but not limited to drug product release and stability that establish and justify the (b) (4) to ensure that the drug product meets the critical quality attributes for intended use throughout the shelf-life.

   We also recommend that you provide data in regard to:

   a. Evaluating the effect of selected in-process pH (b) (4) of the drug product during manufacturing process and on storage (b) (4)

   b. The extent of (b) (4) drug product on storage by analyzing samples from either completed or currently ongoing stability studies.

   c. Chiral stability-indicating HPLC method and its validation report for evaluation.

   If the data convincingly demonstrate that (b) (4) is mainly attributed to the (b) (4) step, you should consider an alternative sterilization process such as (b) (4)

[redacted] (b) (4)

2. Provide a description and controls for the preparation of epinephrine solution in [redacted] (b) (4) employed in compounding bulk drug product solution.

3. The manufacturing process as described does not include verification of the epinephrine content at any stage. We recommend that you incorporate in-process testing of the bulk drug product solution for epinephrine content with appropriate acceptance limits during manufacturing prior to filling.

4. The HPLC analytical method for the assay of epinephrine and related substances employed in generating batch release and stability data presented in your application does not meet the system suitability requirements for intended use.

   For example, the HPLC analytical method currently employed for the assay of epinephrine and related substances of drug product batches (Section 3.2.P.5.2.6) as described show that system suitability criteria are inadequate as: i) the standard concentration is not verified with second standard preparation in all three methods, and ii) in the present version, %RSD is determined based on three standard injections instead of a minimum of five injections as recommended per USP<621>. Additionally, review of method validation information for the current method shows that:

   a. Data presented for precision correspond to analysis of six replicate injections of a single assay solution, and two related substances, [redacted] (b) (4) and [redacted] (b) (4) establishing instrument/injection precision (part of system suitability) instead of method precision, i.e. analysis of six replicate sample preparations.

   b. While data presented for intermediate precision correspond to three replicates for each of Epinephrine, [redacted] (b) (4) and [redacted] (b) (4) by two analysts and on two days, it was not clear if these data were from single injections of three preparations or three injections of a single sample preparation.

   Finally, stability data presented for the drug product batches (manufactured and placed on stability at the same time) show consistently large variations in assay values across all three batches. These almost identical variations in assay values observed at each interval seen for the three batches are most likely due to failure to verify the standard concentration as part of system suitability for the method.

   We recommend that you appropriately revise the analytical method for assay of epinephrine and related substances and revalidate following the Guidance for Industry, "Analytical Procedures and Methods Validation: Chemistry, Manufacturing and Controls Documentation" for ensuring the quality of Epinephrine injection in terms of its identity, purity, strength and potency of L-Epinephrine at release and during its shelf-life.

LABELING

Submit draft labeling that incorporates revisions in the attached labeling. In addition, submit updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations that support any proposed changes.

Please submit draft carton and container labeling revised as follows:

A. General Comments for Container Labels and Carton Labeling

1. Revise the proprietary name and established name to appear in title case.
2. Revise the order for the statement of strength so the mg/mL is the primary expression of strength (not the ratio 1:1000).
3. Present the number 1000 with a comma to help differentiate it from the number 10000 (the other strength of epinephrine).
4. Present the proprietary name, established name, and strength in a stacked format, similar to the following:

Tradename
(Epinephrine Injection, USP)
1 mg/mL
(1:1,000)

5. Ensure that the established name is at least half the size of the proprietary name. Ensure the established name has prominence commensurate with the proprietary name taking into account all pertinent factors including typography, layout, contrast and other printing features per 21 CFR 201.10(g)(2).
6. Increase the prominence of the route of administration statement and relocate it directly below the strength statement. In addition, replace the word (b) (4) with the word "Infusion" in the statement that begins with "For Intravenous (b) (4) to improve clarity of the intended route of administration given that epinephrine is currently given by multiple routes of administration for other indications.
7. Delete the phrase (b) (4) (that follows the route of administration statement) to reduce clutter on this small label. Accordingly, revise the statement to read "For Intravenous Infusion."
8. In order to ensure proper administration of epinephrine of diluting prior to intravenous infusion, we recommend adding the statement "Dilute Before Intravenous Infusion". If space permits, prominently display this statement on the principal display panel under the strength statement.
9. Decrease the prominence of the "Rx Only" statement and relocate the statement to the side panel to minimize distraction from other more important information on the principle display panel.
10. Delete the (b) (4) located on the principal display panel as it is redundant as it is already found on the side panel.
11. Delete the statement "Contains No Sulfites" found on the principle display panel to reduce clutter on a crowded small label.
12. Add the statement "Single Dose Ampule" to the bottom of the principle display panel.
13. Remove the color block from the proprietary name and strength expressions to enhance the contrast and improve readability of the establish name since it is currently difficult to read the established name.

B. Container Label-1 mL Ampule

1. Relocate the (b) (4) statement to the side panel to reduce clutter on a crowded small label.

2. Consider deleting the [redacted] (b) (4) statement which will provide additional space to enlarge the area of the principle display panel.

C. Carton Labeling-1 mL (10 Ampules)

1. Unbold and revise the net quantity statement to read "10 Single-Dose Ampules x1 mL each". Relocate this statement to the lower portion of the principle display panel to avoid competing with the strength statement.
2. Relocate the "preservative free" statement from the top to the bottom of the principal display panel. Delete the "Contains no sulfites" statement.
3. Delete or minimize and relocate the graphic away from the proprietary name to avoid misinterpretation as a letter 'O' in the proprietary name.
4. Increase the prominence of the strength statement since the purple box is difficult to discern against a dark blue background.
5. Relocate the storage condition statement to the side panel to reduce clutter on the principal display panel.
6. If space is needed to accommodate the additional statements, consider relocating the "Each mL contains…" statement from below the strength statement to the side panel.
7. Revise the storage condition statement to include the units °C or °F, respectively, and replace the hyphen within the temperature designations with the word "to" for improved clarity and to be consistent with USP standards. We recommend not using the hyphen between the numbers because a hyphen can be misinterpreted as a minus sign when discussing temperatures. Therefore, revise the storage statement to read "Store between [redacted] (b) (4) to 25°C ([redacted] (b) (4) to 77°F)".
8. Revise the statement after the word" WARNINGS" to appear in mixed case to enhance the readability of the statement "Do not use if discolored or precipitated."
9. Debold the storage statement "Store between …" to improve readability.

REQUIRED PEDIATRIC ASSESSMENTS

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

We note that you have requested a full waiver of pediatric studies because studies are impossible or highly impractical. We do not agree that such studies are impossible or highly impractical. In addition, we believe there are sufficient data available in the literature to assess the safety and effectiveness of epinephrine for the claimed indication in pediatric patients. Therefore, your request for a waiver of pediatric studies is denied. Please submit information from all available sources, including literature, to appropriately label this product for the pediatric population.

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.
    - 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.

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, call Russell Fortney, Regulatory Project Manager at (301) 796-1068.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE: Draft Labeling

23 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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
10/04/2013