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RESEARCH**

APPLICATION NUMBER:

204485Orig1s000

OTHER ACTION LETTERS



NDA 204485

COMPLETE RESPONSE

JHP Pharmaceuticals, LLC
Attention: Mr. Gerald Vasquez
Morris Corporate Center 2
One Upper Pond Road
Building D, 3rd Floor
Parsippany, NJ 07054

Dear Mr. Vasquez:

Please refer to your New Drug Application (NDA) dated September 25, 2012, received September 26, 2012, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Pitressin (vasopressin) Injection, 1 ml vial (20 pressor units).

We acknowledge receipt of your amendments dated November 29, December 5, 6, and 13, 2012 and January 31, February 15, March 7, April 1, 5, and 15, May 5 and 17, June 21 and 24, July 11 and 12, 2013.

We also acknowledge receipt of your amendments dated July 11 and 12, 2013, which were not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

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

Drug Substance

1. The proposed specification for vasopressin is not sufficient for release of drug substance. Include the following tests and acceptance criteria in the specification: identification by amino acid analysis, specific optical rotation, each specified identified impurity with the proposed acceptance criteria (including any unidentified impurity with its proposed limit), peptide content, heavy metals and total microbial aerobic count.
2. Include acceptance criteria for Identification A and Identification B in the drug substance specification.

3. To prove the proper structure of the vasopressin with its disulfide bridge, conduct a bioassay as a one-time characterization study of vasopressin, and correlate it with the HPLC test method used for the assay.
4. Optimize HPLC Method 20456 for Assay and Ordinary Impurities to be capable of resolution, detection and quantification of identified and unidentified impurities. Provide relative retention time for these impurities, and chromatograms that demonstrate resolution of individual impurities. Include validation of this method for suitability of determination of individual vasopressin impurities.
5. Provide a description and validation of additional non-compendial analytical methods requested for complete specification for the drug substance vasopressin.
6. Explain the decrease in Total Impurities from (b) (4) % to (b) (4) % over (b) (4) years for vasopressin batch VP1002-1, as shown in JHP's Certificate of Analysis (COA) compared to (b) (4) COA. Explain the increase in Assay levels of batches VP1001 and VP1002-1 shown in JHP's COAs (b) (4) as compared to (b) (4) COAs (b) (4).

Drug Product

7. Include a test and acceptance criterion for pH (b) (4) during Pitressin (vasopressin) manufacture.
8. Include an additional acceptance criterion for the Description test in the drug product specifications as follows: "Essentially free of visible particulates".
9. Revise limit of NLT (b) (4) ml to NLT (b) (4) ml for "Volume in Container" Test for 3 ml multi-dose vials in the drug product specifications as per requirement of USP <1> for multi-dose containers.
10. The acceptance criterion of (b) (4) % for shelf-life assay is not acceptable; it should comply with that of USP monograph for Vasopressin Injection.
11. Identification by HPLC retention time in the drug product specification is not specific. Include either a specific test, e.g., molecular mass by mass-spectrometry or another nonspecific test.
12. To support safety of the specification limit of NMT (b) (4) % for impurity (b) (4), provide levels of impurity (b) (4) in the historical marketed Pitressin (vasopressin) batches, and/or in the other marketed vasopressin products.
13. Include individual specified identified impurities (b) (4), and (b) (4) with individual shelf-life limits of NMT (b) (4) % in the drug product specifications.

14. The specification limit of NMT (b) (4) % - (b) (4) % for individual unidentified impurities of (b) (4) is not acceptable. All impurities with level of > (b) (4) % should be identified. Therefore, set the limit for individual unidentified impurities as NMT (b) (4) %.
15. Provide results of linearity and accuracy evaluation for all known vasopressin degradation products in the validation of analytical method 20545.
16. We noted that you included testing in upright or inverted vials positions in the stability protocols for long-term, accelerated and intermediate testing of drug product. Revise the stability protocols to clarify that testing in inverted vials positions will be performed or provide comparative data showing that upright and inverted samples have comparative stability.
17. Provide results of In-use testing for aged multi-dose vials that were stored for the maximal current storage time.
18. Since stability data under accelerated storage conditions showed significant changes, include stability testing for the first three validation lots (manufactured without an overage) at the intermediate conditions in the post-approval stability commitment. Provide post approval stability protocols for testing at intermediate conditions, if different from the stability studies protocol.
19. For your claim of Categorical Exclusion, provide additional statement that, “to the best of JHP Pharmaceuticals LLC knowledge, no extraordinary circumstances exist”.
20. The 9-month stability data that you have provided for drug product without overages is not sufficient for granting a viable expiration dating period. Moreover, the stability data show that the room temperature storage may not be appropriate to maintain the USP assay limit of 90 – 110% for this product over a commercially viable period. Therefore, we recommend that you generate stability data at lower storage temperature of (b) (4) °C for the drug product.

CLINICAL PHARMACOLOGY

Stability of AVP in diluents other than isosaline and dextrose

The diluent used for diluting AVP prior to infusion is not stated in most of the publications reporting on clinical trials. The stability of AVP was tested by the sponsor in only 2 diluents: isosaline and 5% dextrose. AVP was found to be stable in isosaline. However, when dissolved in 5% dextrose AVP was unstable. The reason for the instability of AVP in 5% dextrose is not known. There is a need to determine the stability of AVP in additional diluents such as, Ringer's, lactated Ringer's, sodium citrate and Plasma-Lyte® in order to exclude the possibility that degradation of AVP occurred in the published trials that did not state the diluents used.

REQUIRED PEDIATRIC ASSESSMENTS

As described in our LABELING PMR/PMC DISCUSSION COMMENTS Letter dated June 26, 2013:

We note that you have requested in your March 6, 2013 submission a full Pediatric Waiver from the requirement for pediatric studies under Section 505B(a)(4)(A) of the Act. However, we believe that additional data in pediatric patients are required. These data may be obtained post-approval as part of a Postmarketing Requirement (PMR) in which you commit to attempt to provide additional information concerning vasopressin effects in pediatric patients by supplying study information (e.g., protocols, datasets, study reports, and safety narratives/case report forms) from the investigators of the published pediatric studies in your submission (e.g., Choong et. al. [2009]). We would need to reach agreement on this PMR before the application can be approved.

Refer to the *Guidance for Industry: How to Comply with the Pediatric Research Equity Act* (September 2005) and submit a pediatric plan to support the deferral of pediatric studies. Your pediatric plan must include the submission date(s) for the pediatric study information you plan to supply.

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, please contact:

Quynh Nguyen, Pharm.D., RAC
Regulatory Project Manager
(301) 796-0510

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

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
07/19/2013