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RESEARCH**

APPLICATION NUMBER:

206628Orig1s000

OTHER ACTION LETTERS



NDA 206628

COMPLETE RESPONSE

HQ Specialty Pharma Corporation
120 Route 17 North
Paramus, NJ 07652

Attention: Joseph Pizza
President

Dear Mr. Pizza:

Please refer to your New Drug Application (NDA) dated May 12, 2014, received May 12, 2014, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Dexmedetomidine Hydrochloride Injection, 400 mcg/4mL and 1000 mcg/10 mL.

We acknowledge receipt of your amendments dated June 12, July 1 and 15, August 12, September 16 and 29, December 1, 15, and 22, 2014, and January 8, February 2, 5, 10, and 18, and March 2, 6, and 9, 2015.

This new drug application provides for the use of Dexmedetomidine Hydrochloride Injection, 400 mcg/4mL and 1000 mcg/10 mL for sedation of non-intubated patients prior to and/or during surgical and other procedures.

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

This application does not provide data that demonstrate the preservative system for the multi-dose vials is effective at the minimum proposed preservative content. The data submitted in the March 6, 2015, amendment did not include USP<51> data on *Escherichia coli*. The justification you have provided that “*E. coli* is appropriate when testing oral preparations but not injections” is unacceptable as the USP<51> compendial test does not allow for alterations to the panel of test organisms.

Information needed to address this deficiency:

As requested in the December 19, 2014, information request, the proposed minimum preservative content should be supported by complete test results from USP<51> Antimicrobial Effectiveness Testing.

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(l)(1)(i)] in structured product labeling (SPL) format as described at

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

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.

POSTMARKETING REQUIREMENTS UNDER 505(o)(3)

As described in our email correspondence dated February 12, 2015, we have determined that, if this application is approved, you will be required to conduct postmarketing study of Dexmedetomidine Hydrochloride to assess a signal of a serious risk.

Specifically, we have determined that, if NDA 206628 is approved, you will be required, pursuant to section 505(o)(3) of the FDCA, to conduct the following:

- 2884-1 Conduct an adequate leachable safety assessment for the (b) (4) rubber stopper used in your container closure system. This assessment must include leachable data from long-term stability studies (taking into consideration the proposed shelf-life) to determine if the identified extractables leach into the drug product over time. Using this information, conduct a toxicological risk assessment justifying the safety of the leachables, taking into consideration the maximum daily dose of the identified materials for this drug product. For your toxicological risk assessment, any leachable that contains a structural alert for mutagenicity should not exceed (b) (4) mcg/day total daily exposure, or it must be adequately qualified for safety. A toxicological risk assessment should be provided for any non-genotoxic leachable that exceeds (b) (4) mcg/day.

The timetable you submitted on February 18, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	03/2015
Study Completion:	06/2018
Final Report Submission:	09/2018

We acknowledge receipt of your protocol dated March 6, 2015, containing your proposed postmarketing study designs to address these issues. We will continue discussion of your proposed postmarketing study as needed.

Any additional specific details of this required postmarketing study, including a timetable and annual reporting requirements, will be described more fully in the approval letter for this application, if it is approved.

If you complete this study prior to re-submitting your application, you may include the final report and relevant data sets in your Complete Response submission to facilitate review of the information.

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>.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Allison Meyer, Regulatory Project Manager, at (301) 796-1258.

Sincerely,

{See appended electronic signature page}

Rigoberto Roca, MD
Deputy Director
Division of Anesthesia, Analgesia,
And Addiction Products
Office of Drug Evaluation II
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/

RIGOBERTO A ROCA
03/12/2015