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RESEARCH**

*APPLICATION NUMBER:*

**22-466**

**OTHER ACTION LETTER(s)**



NDA 022466

**COMPLETE RESPONSE**

Pierrel S.p.A.  
c/o TechReg Services, Inc  
17 McIntire Drive  
Hillsborough, NJ 08844

Attention: Steven Pikulin, Ph.D., RAC  
US Agent for Pierrel S.p.A.

Dear Dr. Pikulin:

Please refer to your new drug application (NDA) dated November 24, 2008, received November 25, 2008, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Articaine Hydrochloride 4% with Epinephrine 1:100,000 and 1:200,000; injection.

We acknowledge receipt of your amendments dated January 5, March 14, June 22, July 11, 13, 20, 25, and August 5, 2009.

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

**FACILITY INSPECTIONS**

During a recent inspection of the Pierrel S.p.A. manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

**PRODUCT QUALITY**

Your application does not contain adequate and normal laboratory controls for the manufacture of these drug products. Provide the following information.

1. A detailed description of the procedure used to (b) (4) the (b) (4) (b) (4)
2. Validation studies demonstrating that the cap and plunger (b) (4) procedure is effective.
3. Validation studies for the (b) (4)
4. The SOP or a description of the SOP for (b) (4) validation that includes a growth promotion test and spore count for (b) (4)

5. Validation studies for [REDACTED] (b) (4)  
[REDACTED] If validation is conducted with glass cartridges of a different size [REDACTED] (b) (4) include a justification for why the results with the alternate cartridges are applicable to the 1.8 mL cartridges.
6. The SOP or a description of the SOP for bioburden determination that includes a growth promotion test for the TSB agar used as a culturing medium.
7. The SOP or a description of the SOP for environmental monitoring that includes validation studies that justify the chosen incubation temperature for testing for yeasts and molds.

## **LABELING**

8. 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>. We reserve additional comments on the proposed labeling until the application is otherwise adequate.
9. Submit draft carton and container labels revised as follows:

### Cartridge Labels

- a. The cartridge labels lack differentiation between the two strengths, since both are blue text on a white background. Use an alternate color (e.g., not blue) for one of the strengths to reduce the potential for confusion between the two strengths.
- b. The net quantity statement (1.8 mL) immediately follows the established name, causing it to appear to be part of the product strength rather than a statement of the net quantity per cartridge. Relocate the net quantity statement to either the bottom of the label or the top left corner of the label, wherever space permits.

### Carton Labels

- c. The carton labeling lacks differentiation between the two strengths because both are yellow in color with a large blue stripe. Use an alternate color (e.g., not blue) for one of the strengths to reduce the potential for confusion between the two strengths.
- d. The blue print on a blue background on the principal display panel is difficult to read. Consider a lighter color for the background or consider a different colored print to improve the readability of the important information on the principal display panel.
- e. Increase the size of the established name so that it is at least one-half the size of the proprietary name in accordance with 21 CFR 201.10(g)(2), which states: the established name shall be printed in letters that are at least half as large as the

letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.

- f. Revise the net quantity statement to read “100 Cartridges each containing 1.8 mL” to more accurately describe the contents of the carton.
- g. Add the following statements to the carton labels:
  - i. For Intraoral Submucosal Injection Only
  - ii. Any unused portion of a cartridge should be discarded.
  - iii. Parental drug products should be inspected visually for particulate matter and discoloration prior to administration.
- h. Revise the statement on the carton labels regarding the storage and handling of the product to the following:
  - i. Store at room temperature; 25°C, excursions permitted between 15°C and 30°C.
- i. On the cartridge and carton labels, revise the drug name and strength below the tradename and established name to read as follows:

**Tradename (articaine hydrochloride and epinephrine) Injection**

**Articaine HCl 4% (40 mg/mL) and epinephrine free base 1:200,000  
(containing epinephrine bitartrate 0.0009 mg/mL)**

**or**

**Articaine HCl 4% (40 mg/mL) and epinephrine free base 1:100,000  
(containing epinephrine bitartrate 0.0018 mg/mL)**

**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 ISSUES**

Several issues pertinent to clarifying the safety or efficacy of this product require additional information. We strongly encourage you to propose studies to address the following issues and to initiate those studies as soon as possible, thereby possibly allowing you to submit the final study reports with your complete response.

1. Investigate the potential for optimizing the sensitivity of the analytical methodology with regard to (b) (4) to determine if either of these impurities is present in the drug substance at levels that would exceed (b) (4). If these impurities exceed (b) (4) then conduct the following studies:
  - a. Conduct an in vitro bacterial reverse mutation assay (Ames assay) with the isolated (b) (4) tested up to the limit dose of the assay.

- b. Conduct an in vitro bacterial reverse mutation assay (Ames assay) with the isolated (b) (4) tested up to the limit dose of the assay.
2. Conduct a stability study to assess long and short term stability for (b) (4) drug product. The goal of the study would be to determine (b) (4) parameters that do not cause product degradation beyond allowed specifications immediately after treatment and over a two year (room temperature) shelf life. For all (b) (4) parameters examined, testing shall be conducted using: (1) samples from three separate product batches; and (2) samples held under long term, intermediate and accelerated storage conditions. We recommend that you evaluate the results using the statistical guidelines described in *Guidance for Industry – QIE Evaluation of Stability Data*.

### **OTHER**

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. 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's *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, contact Ayanna Augustus, Regulatory Project Manager, at [ayanna.augustus@hhs.fda.gov](mailto:ayanna.augustus@hhs.fda.gov) (301) 796-3980.

Sincerely,

*{See appended electronic signature page}*

Bob A. Rappaport, M.D.  
Director  
Division of Anesthesia, Analgesia,  
and Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure --Package Insert

5 pages of draft labeling has been withheld in full as B(4) CCI/TS immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22466	ORIG-1	PIERREL S.P.A.	ARTICAINE 4% /EPINEPHRINE 1:20000 INJ

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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.**

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/s/

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BOB A RAPPAPORT  
09/25/2009