

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-466**

**SUMMARY REVIEW**



**Food and Drug Administration**  
**CENTER FOR DRUG EVALUATION AND RESEARCH**  
 Division of Anesthesia, Analgesia, and Rheumatology Products  
 10903 New Hampshire Ave.  
 Silver Spring, MD 20993-0002

**Summary Review for Regulatory Action**

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| <b>Date</b>                                       | February 26, 2010  |
| <b>From</b>                                       | Rigoberto Roca, M.D.   |
| <b>Subject</b>                                    | Deputy Division Director Summary Review  |
| <b>NDA Number</b>                                 | 22-466   |
| <b>Applicant Name</b>                             | Pierrel,S.p.A  |
| <b>Date of Original Submission</b>                | November 25, 2008<br>Complete Response letter issued September 25, 2009  |
| <b>Date of Complete Response Submission</b>       | December 29, 2009  |
| <b>PDUFA Goal Date</b>                            | February 28, 2010  |
| <b>Proprietary Name / Established (USAN) Name</b> | Articaine hydrochloride with epinephrine   |
| <b>Dosage Forms / Strength</b>                    | Articaine hydrochloride and epinephrine for injection<br>Articaine: 4% (40 mg/mL)<br>Epinephrine: 1:100,000 (10 mcg/mL) and 1:200,000 (5 mcg/mL) |
| <b>Proposed Indication</b>                        | For local, infiltrative or conductive anesthesia in both simple and complex dental (b) (4) procedures  |
| <b>Action</b>                                     | <i>Approval</i>  |

|                                     |  |
|-------------------------------------|--|
| <b>Material Reviewed/Consulted</b>  |  |
| OND Action Package, including:      |  |
| Medical Officer Review              | NA   |
| Statistical Review                  | NA   |
| Pharmacology Toxicology Review      | Carlic K. Huynh, Ph.D.; R. Daniel Mellon, Ph.D.                    |
| CMC Review                          | Elsbeth Chikhale, Ph.D.; Prasad Peri, Ph.D.                        |
| Clinical Pharmacology Review        | Srikanth C. Nallani, Ph.D.; Suresh Doddapaneni, Ph.D.              |
| Product Quality Microbiology Review | Steven E. Fong, Ph.D.; James McVey, Ph.D.;<br>David Hussong, Ph.D. |
| DDMAC                               | Mathilda Fienkeng  |
| OSE/DMEPA                           | Tselaine Jones-Smith, Pharm.D.;<br>Kristina Arnwine, Pharm.D.      |

CDTL = Cross-Discipline Team Leader  
 CMC = Chemistry, Manufacturing, and Controls  
 DDMAC = Division of Drug Marketing, Advertising and Communication

DMEPA = Division of Medication Error Prevention and Analysis  
 OND = Office of New Drugs  
 OSE = Office of Surveillance and Epidemiology

## 1. Introduction

Pierrel S.p.A. submitted NDA 22-466 for marketing approval of two formulation presentations of articaine hydrochloride 4% with epinephrine (1:100,000 and 1:200,000) on November 25, 2008. The requested indication for both products was for local, infiltrative, or conductive anesthesia in simple and complex dental procedures. The NDA was a 505(b)(2) application referencing two approved formulations of Septocaine, NDA 20-971 (articaine with epinephrine 1:100,000) and NDA 22-010 (articaine with epinephrine 1:200,000).

The application received a Complete Response letter on September 25, 2009, due to numerous deficiencies identified at the product manufacturing site by inspectors from the Office of Compliance.

This review will provide an overview of the regulatory and scientific facts of this Complete Response submission and issues that were identified during the course of the review. Aspects that will be touched upon include the regulatory history and the adequacy of the data to support the application.

## 2. Background

Articaine hydrochloride is a local anesthetic of the amide class, first approved in Europe in 1976. Septocaine was approved for marketing in the United States in 2000. Articaine differs from other drugs in this class in that it contains a thiophene ring instead of a (b) (4) which increases its lipid solubility.

As noted in Dr. Rappaport's review dated September 25, 2009, the epinephrine is added to provide vasoconstriction, prolonging local tissue concentrations of the anesthetic and extending the duration of action. The epinephrine also acts to reduce the possibility of systemic toxicity related to the rapid absorption of the local anesthetic.

During the first cycle review, the following issues were identified regarding the differences in the product's formulation compared to the referenced drug:

- Fill volume: The fill volume of the referenced products was 1.7 mL, while the fill volume of the new products was 1.8 mL.
- NaCl Content: The referenced drug products contained 1.6 mg/mL of NaCl, while the new products contained 1.0 mg/mL. While exceptions to the regulations regarding the excipients in generic formulations include preservatives, buffers and antioxidants, NaCl does not fall into any of these categories.
- pH: The proposed product would be pH adjusted with hydrochloric acid rather than sodium hydroxide which was used for the referenced drug products.

Each of these issues was resolved to the satisfaction of the review team during the first review cycle (see Dr. Rappaport's, Dr. Nikhar's, and Dr. Chikhale's reviews).

The Complete Response letter dated September 25, 2009, identified the following requirements that would need to be addressed in order to achieve an acceptable level of microbiological control:

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) 2
5. Validation studies for (b) (4) Page 2  
If validation is conducted with glass cartridges of a different size (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.

Three additional issues were identified in the course of the first review cycle; however, their resolution was not required for approval and could, therefore, be conducted as post-marketing studies. They were included in the Complete Response letter and the Applicant was encouraged to address the issues and initiate the studies as soon as possible in order to potentially allow them to submit the final study reports as part of the complete responses.

These issues are noted immediately below, and are further addressed in review under the specific discipline:

- 1) Investigation of the potential for optimizing the sensitivity of the analytical methodology with regard to (b) (4) (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 the following studies would need to be conducted:
  - a) An in vitro bacterial reverse mutation assay (Ames assay) with the isolated (b) (4) (b) (4), tested up to the limit dose of the assay.
  - b) An in vitro bacterial reverse mutation assay (Ames assay) with the isolated (b) (4) (b) (4), tested up to the limit dose of the assay.

- 2) Conduct of a stability study to assess long and short term stability for (b) (4) (b) (4) drug product. The goal of the study would be to determine (b) (4) (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*.

### 3. Chemistry, Manufacturing, and Controls (CMC)

Differences between the Applicant's product and the referenced drug that were identified and addressed during the first review cycle included:

- Difference in the fill volume.
- Difference in the NaCl content.
- Difference in the pH
- Difference in the method of sterilization

As noted in Dr. Rappaport's, Dr. Nikhar's, and Dr. Chikhale's reviews, the first three issues were reviewed and satisfactory resolutions were reached by the review team during the first review cycle.

(b) (4) (b) (4) Although this difference in sterilization technique was not deemed to be an issue that would preclude approval, the CMC review team recommended that the Applicant perform a post-marketing study to evaluate a modified (b) (4) per International Conference on Harmonization (ICH) standards. This request was conveyed to the Applicant in the CR letter issued on September 25, 2009.

In this submission, the Applicant submitted details on the (b) (4) studies that are being proposed to be performed to fulfill the post-marketing commitment. As noted in Dr. Fong's review, (b) (4) parameters appeared to be a reasonable approach to develop a method that would not adversely affect the short- and long-term stability of the product and, subsequently, fulfill the post-marketing commitment. The Applicant indicated in this submission that a final report of the stability studies will be submitted by January 31, 2013.

An unresolved issue during the first cycle was the overall withhold recommendation that was issued by the Office of Compliance after they concluded their site inspections at the Applicant's Capua, Italy, manufacturing facility site. The deficiencies conveyed in the CR letter issued on September 25, 2009, have been adequately addressed by the Applicant in this

submission and the concerns identified by the CMC and Microbiology reviewers have been resolved.

As noted in Dr. Chikhale's review, the Office of Compliance has given an overall Acceptable recommendation for the NDA.

#### Outstanding or Unresolved Issues

I concur with the conclusions reached by the chemistry reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. Stability testing demonstrated that the current products remain stable under normal and accelerated storage conditions, supporting a 24-month expiry period. There are no outstanding issues that would preclude approval.

## **4. Nonclinical Pharmacology/Toxicology**

There were ten potential impurities identified in the articaine hydrochloride drug substance. Only one of those impurities was above ICH identification levels and it was within acceptable limits per ICH guidelines in the drug products. Two of the impurities contain structural alerts: (b) (4) During the first review cycle, it was noted that the quantitative structure-activity relationship (QSAR) analysis by CDER's Informatics and Computational Safety Analysis Staff (ICSAS) predicted that they would have low genotoxic potential. These two impurities were not detected in the drug products by assays acceptable to the Agency. In addition, they did not appear to be degradants, but rather process-related impurities, according to the Applicant, and the review team agreed with this conclusion.

The review team found the application to be acceptable for approval, with the recommendation that post-marketing commitment studies intended to develop improved detection and characterization of (b) (4) should be requested.

These studies were conducted by the Applicant, and the results were submitted as part of the complete response. The review team has determined that the Applicant has provided adequate data to conclude that (b) (4) are not mutagenic. The Sponsor has addressed and resolved the previously recommended postmarketing commitment as part of the complete response. From a nonclinical pharmacology toxicology perspective, NDA 22-466 may be approved with no post marketing studies required at this time.

I concur with the conclusions reached by the pharmacology/toxicology reviewers that there are no outstanding pharmacology/toxicology issues that preclude approval.

## **5. Clinical Pharmacology/Biopharmaceutics**

As noted in Dr. Rappaport's review, the clinical pharmacology/biopharmaceutics review team found the application to be acceptable for approval during the first cycle. The question raised by Dr. Marroum in his review regarding whether the difference in pH between the Applicant's formulation and the referenced drug resulted in differential uptake into the nerve was

addressed by the Applicant's study of the pH of the referenced drug products, which demonstrated that the pH of the those products were actually the same as the pH of the new formulations at the time the drug would be administered to the patient.

I concur with the conclusions reached by the reviewers that there are no outstanding clinical pharmacology issues that preclude approval.

## **6. Clinical Microbiology**

The product is not a therapeutic antimicrobial; therefore, clinical microbiology data were not required or submitted for this application.

## **7. Clinical/Statistical-Efficacy**

As noted in Dr. Rappaport's review, no new efficacy data was submitted in support of this application. The applicant is depending on their 505(b)(2) reference, which was acceptable during the first cycle review, and remains so.

## **8. Safety**

As noted in Dr. Rappaport's review, no new safety data was generated for this application. In the first cycle review, Dr. Nikhar provided a summary of the safety profile of the referenced drug, which should be identical to that of these new formulations. She recommended the addition of certain adverse events (hypoesthesia, paralysis of ocular muscles, ischemic injury and necrosis) to the products' labels based on recent reports of these events seen with the referenced drug. A request will also be sent to the RD application holder to update their labels with these additional reported adverse events.

## **9. Advisory Committee Meeting**

As was noted in Dr. Rappaport's review, the convening of an advisory committee meeting for discussion of this application was deemed to be unnecessary. There was no new clinical experience and no product concerns that would require discussion at an advisory committee meeting.

## **10. Pediatrics**

As noted in Dr. Rappaport's review, this product is exempt from the pediatric study requirements authorized by PREA.

## **11. Other Relevant Regulatory Issues**

There are no other unresolved relevant regulatory issues.

## 12. Labeling

The Applicant has agreed to the labeling modifications that were included with the Complete Response letter that was issued on September 25, 2009. Representatives from the Office of Surveillance and Epidemiology were consulted during this review cycle and their recommendations were incorporated during the discussion of the label.

## 13. Decision/Action/Risk Benefit Assessment

Regulatory Action  
Approval.

### Risk:Benefit Assessment

During the first-cycle review, the review team had concluded that the Applicant had demonstrated that these new formulations of articaine and epinephrine had a favorable risk:benefit ratio when used according to the labeled instructions, and that the application had met the requirements for 505(b)(2) products.

The inability to approve the application during the first cycle was due to the overall withhold recommendation issued by the Office of Compliance after their site inspections identified numerous deficiencies in microbiological controls at the product manufacturing site. The Office of Compliance has reviewed the information in the Complete Response submission, and has issued an overall Acceptable recommendation for the NDA; therefore, my overall risk:benefit assessment is in favor of approval of this application.

Recommendation for Post-marketing Risk Management Activities  
None.

### Recommendation for other Post-marketing Study Commitments

Conduct short and long term stability studies on (b) (4) product.

| Application<br>Type/Number | Submission<br>Type/Number | Submitter Name          | Product Name                                      |
|----------------------------|---------------------------|-------------------------|---|
| -----<br>NDA-22466         | -----<br>ORIG-1           | -----<br>PIERREL S.P.A. | -----<br>ARTICAINE 4% /EPINEPHRINE<br>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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RIGOBERTO A ROCA  
02/26/2010