

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-466

APPROVAL LETTER



NDA 022466

NDA APPROVAL

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 TRADENAME (articaine hydrochloride and epinephrine) Injection, to be marketed in the following strengths:

Articaine hydrochloride 4% and epinephrine 1:200,000,
Articaine hydrochloride 4% and epinephrine 1:100,000.

We acknowledge receipt of your submissions dated January 5, March 14, June 22, July 11, 13, 20, and 25, August 5, December 28, 2009, January 15, and 26, and February 4, and 9, 2010.

The December 28, 2009, submission constituted a complete response to our September 25, 2009, action letter.

This new drug application provides for the use of TRADENAME (articaine hydrochloride and epinephrine) Injection for local, infiltrative, or conductive anesthesia in both simple and complex dental procedures.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text for the package insert and with the minor editorial revisions listed below for the Carton and Immediate Container labels.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical to the enclosed labeling text for the package insert. For administrative purposes, please designate this submission, "**SPL for approved NDA 022466.**"

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate-container labels as soon as they are available but no more than 30 days after they are printed that are identical to the enclosed draft labels, with the following minor editorial revisions agreed to between you and Ayanna Augustus from the FDA on February 23, 2010.

Carton Labels

1. Ensure that the product strengths are presented in the same format throughout the carton labeling:

Articaine hydrochloride 4% and epinephrine 1:200,000
Articaine hydrochloride 4% and epinephrine 1:100,000

2. We acknowledge your agreement to increase the prominence of the established name once a proprietary name is established and deemed acceptable. However, if you market this product without a tradename, 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.”
3. Revise the labeling to include the ‘Rx only’ on the side panel.
4. Correct the typographical error on the carton labeling for the product strengths of epinephrine bitartrate per milliliter. The correct strengths are 0.009 mg/mL for epinephrine 1:200,000 and 0.018 mg/mL for epinephrine 1:100,000.

Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 022466.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

PROPRIETARY NAME

If you choose to use a proprietary name for this product, the name and its use in the labels must conform to the specifications under 21 CFR 201.10 and 201.15. We recommend that you submit any proprietary name to the Agency for our review prior to its implementation.

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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

This product is appropriately labeled for use in ages 4 years to 16 years for local, infiltrative, or conductive anesthesia in both simple and complex dental procedures indications. Therefore, no additional studies are needed in this pediatric group.

POSTMARKETING COMMITMENTS

We remind you of your postmarketing study commitment in your submission dated December 28, 2009. This commitment is listed below.

- 1595 Conduct a stability study to assess long and short term stability for (b) (4) (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 – Q1E Evaluation of Stability Data*.

Final Report Submission: by January 31, 2013

Submit clinical and nonclinical protocols to your IND for this product. Submit chemistry, manufacturing, and controls (CMC) protocols and all final study reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments should be prominently labeled “**Postmarketing Study Commitment Protocol**,” “**Postmarketing Study Commitment Final Report**,” or “**Postmarketing Study Commitment Correspondence**.”

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

Please submit one market package of the drug product when it is available.

EXPIRATION DATING PERIOD

An expiration dating period of 24 months is approved for TRADENAME (articaine hydrochloride and epinephrine) Injection; articaine hydrochloride 4% and epinephrine 1:200,000, and articaine hydrochloride 4% and epinephrine 1:100,000, stored at 25°C (77°F); brief excursions permitted between 15-30°C (59-86°F).

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety-related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B-05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, contact Ayanna Augustus, Ph.D., Regulatory Project Manager, at ayanna.augustus@fda.hhs.gov or (301) 796-3980.

Sincerely,

{See appended electronic signature page}

Rigoberto Roca, M.D.
Deputy Director
Division of Anesthesia, Analgesia,
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Package Insert
 Carton and Container Labels

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

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
02/26/2010