

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-466**

**CHEMISTRY REVIEW(S)**

**NDA 22-466**

**Tradename™  
(articaine HCl and epinephrine bitartrate)  
Injection**

**Pierrel S.p.A.**

**Elsbeth Chikhale, Ph.D.  
ONDQA – DPA I – Branch II  
for  
Division of Anesthesia, Analgesia and Rheumatology  
Products**

Due to the change in the Microbiology Review recommendation for this NDA (see microbiology review no. 2, dated Spetmber 18, 2009), this is a revised summary review which supercedes review no. 1 dated 09/02/09

**NDA 22-466**  
**Trade Name**  
**(articaine HCl and epinephrine bitartrate)**  
**Injection**

**Summary of the Basis for the Recommended Action  
from Chemistry, Manufacturing, and Controls**

**Applicant:** Pierrel S.p.A.

**Indication:** For local, infiltrative or conductive anesthesia in both simple and complex dental (b) (4) procedures.

**Presentation:** The drug product is a sterile aqueous solution for injection formulated with 4% (w/v) articaine hydrochloride, containing either 0.0018% (w/v) or 0.0009% (w/v) epinephrine bitartrate (equivalent to 1:100000 (w/v) and 1:200000 (w/v) concentration of epinephrine as the free base) packaged in USP Type I clear glass cartridges, filled to nominally contain 1.8 mL per cartridge and closed with a (b) (4)

<b>EER Status:</b>	Recommendations:	Withhold
<b>Consults:</b>	EA -	Categorical exclusion provided
	CDRH-	N/A
	Statistics -	N/A
	Methods Validation -	Not recommended
	DMEPA-	Completed
	Biopharm-	N/A
	Microbiology -	Acceptable
	Pharm/toxicology -	N/A

**Original Submission:** 24-November-2008

**Re-submissions:** N/A

**Post-Approval CMC: PMC/PMR:** Microbiolog review indicated that the

sponsor will be required to conduct  
 <sup>(b) (4)</sup> feasibility  
studies.

**Background:**

This NDA is submitted as a 505(b)(2) application. The reference drug is Septocaine® (articaine hydrochloride and epinephrine bitartrate) Injection; NDA 22-010 (1:200,000 w/v epinephrine) and NDA 20-971 (1:100,000 w/v epinephrine).

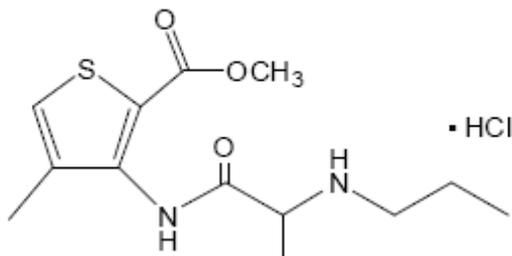
**Drug Substances:****Articaine Hydrochloride:**

The drug substance, Articaine HCl, is a previously approved drug substance, produced by chemical synthesis. All information regarding the physicochemical properties, impurities, method of synthesis and purification, process controls, control of raw materials, container closure system and stability of articaine HCl are provided in the Drug Master File (b) (4) held by (b) (4) DMF (b) (4) was reviewed and found adequate in support of this NDA. However, two possibly mutagenic impurities (b) (4) were discussed with the pharmacology/toxicology reviewer and the applicant was asked to justify the levels of these impurities in the drug substance. The applicant has provided a satisfactory response and the levels of these impurities are believed to be safe as indicated by the pharmacology/ toxicology review.

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

**Articaine hydrochloride:**

**Chemical Name:** Methyl 4-methyl-3-[[[(2R)-2-(propylamino)propanoyl] amino]thiophene-2-carboxylate hydrochloride;



Molecular formula: C<sub>13</sub>H<sub>21</sub>ClN<sub>2</sub>O<sub>3</sub>S (C<sub>13</sub>H<sub>20</sub>N<sub>2</sub>O<sub>3</sub>S•HCl)

Molecular weight: 320.84

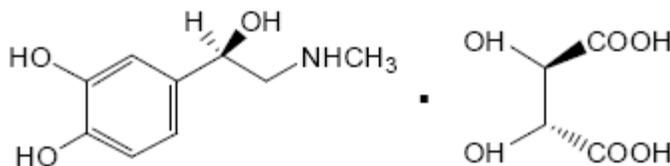
**Epinephrine bitartrate:**

The drug substance, epinephrine bitartrate, is a previously approved drug substance, produced by chemical synthesis. All information regarding the physicochemical properties, impurities, method of synthesis and purification, process controls, control of raw materials, container closure system and stability of epinephrine bitartrate are provided in DMFs (b) (4). Both DMFs were reviewed and found adequate.

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

**Chemical Name:** 1,2-Benzenediol, 4-[1-hydroxy-2-(methylamino)ethyl]-, (R)-, [R-(R\*,R\*)]-2,3-dihydroxybutanedioate (1:1) (salt);

**Structural Formula**



Molecular Formula: Molecular formula:  $C_{13}H_{19}NO_9$  ( $C_9H_{13}NO_3 \cdot C_4H_6O_6$ )

Molecular Weight: 333.3 g/mol (bitartrate salt)

Molecular Weight: 183.2 g/mol (free base)

### Conclusion

The drug substances are satisfactory

### Drug Product:

The proposed drug product is a sterile solution for injection, indicated for local, infiltrative or conductive anesthesia in both simple and complex dental <sup>(b) (4)</sup> procedures. The route of administration is intra-tissue injection. The drug product is formulated as a sterile aqueous solution for injection with 4% (w/v) articaine hydrochloride, containing either 0.0018% (w/v) or 0.0009% (w/v) epinephrine bitartrate (equivalent to 1:100000 (w/v) and 1:200000 (w/v) concentration of epinephrine as the free base) in a single use USP Type I clear glass cartridges, filled to nominally contain 1.8 mL per cartridge and closed with <sup>(b) (4)</sup>

The excipients consist of Sodium Chloride USP; Sodium Metabisulfite NF; Hydrochloric Acid NF; and Water for Injection USP.

The manufacturing process is performed under <sup>(b) (4)</sup>

Specifications for the drug product include appearance, identity, pH, volume, assay, related substances, sodium metabisulfite assay, particulates, sterility, and bacterial endotoxins.

**Conclusion:** The drug product is satisfactory.

**Comment**

On August 7, 2009, the application was recommended for approval from microbiology quality standpoint (see review#1 by Steven Fong, Ph.D. dated August 7, 2009). However, on September 18, 2009, a memorandum was filed by the Microbiology Reviewer (see review#2 by Steven Fong, Ph.D. dated September 18, 2009) and concluded that, due to deficiencies related micro in the inspection report, the microbiology recommendation has been revised from approval (review no. 1) to withheld (review no. 2).

**Establishment Evaluation Report (EER)**

The cGMP status/overall recommendation for this application is **WITHHOLD**. The cGMP inspection revealed defects and deficiencies related to the integrity of the Microbiological Control aspects of the drug product.

**Overall Conclusion:**

From a CMC perspective, the application is not approvable based on the withhold recommendation from office of compliance with respect to cGMP microbiology issues related to the drug product manufacturing site and the non-satisfactory recommendation from the microbiology reviewer (review no. 2, dated September 18, 2009).

Ali Al-Hakim, Ph.D.  
Branch Chief,  
DPA I/ONDQA

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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ALI H AL HAKIM  
09/24/2009

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# Chemistry Review Data Sheet

1. NDA 22-466
2. REVIEW #: 1
3. REVIEW DATE: 14-AUG-2009
4. REVIEWER: Elsbeth Chikhale, Ph.D.
5. PREVIOUS DOCUMENTS: N/A
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	24-NOV-2008
Amendment to original <sup>1</sup>	14-MAR-2009
Amendment to original <sup>2</sup>	13-JUL-2009

  - 1) The 3/14/09 amendment provides for a response to Agency comments in the filling communication dated 2/3/09.
  - 2) The 7/13/09 amendment provides for responses to the Agency's information requests.
7. NAME & ADDRESS OF APPLICANT:

Name: Pierrel S.p.A.

Address: Via A. Saffi, 25  
20123 Milan, Italy

Representative: Steven Pikulin, US Agent for Pierrel S.p.A.

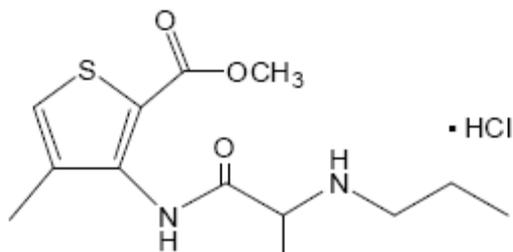
Telephone: (908) 359 – 7791
8. DRUG PRODUCT NAME/CODE/TYPE:
  - a) Proprietary Name: Tradename™
  - b) Non-Proprietary Name (USAN): articaïne HCl and epinephrine
  - c) Code Name/#:
  - d) Chem. Type/Submission Priority:
    - Chem. Type: 5 (new formulation)
    - Submission Priority: Standard

## Chemistry Review Data Sheet

9. **LEGAL BASIS FOR SUBMISSION:** This NDA is submitted as a 505(b)(2) application. The reference drug is Septocaine® (articaine hydrochloride and epinephrine bitartrate) Injection; NDA 22-010 (1:200,000 w/v epinephrine) and NDA 20-971 (1:100,000 w/v epinephrine).
10. **PHARMACOL. CATEGORY:**  
Articaine HCl is a local anesthetic, belonging to the amino amide class of local anesthetics. Epinephrine is a vasoconstrictor added to articaine HCl to slow absorption of articaine into the general circulation and thus prolonging articaine's tissue concentration at the site of action.
11. **DOSAGE FORM:** Injection
12. **STRENGTH/POTENCY:** 40 mg/mL articaine HCl and 5 or 10 µg/mL epinephrine (free base).
13. **ROUTE OF ADMINISTRATION:** Intra-tissue injection
14. **Rx/OTC DISPENSED:**  Rx       OTC
15. **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):**  
 SPOTS product  Form Completed  
 Not a SPOTS product

## Chemistry Review Data Sheet

## 1. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

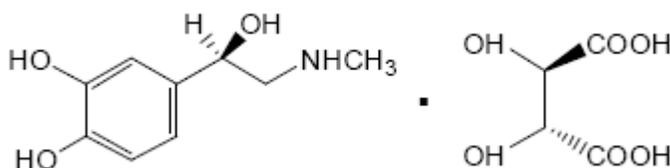
**Articaine hydrochloride:**

Chemical names:

1. Methyl 4-methyl-3-[[*(2RS)*-2-(propylamino)propanoyl] amino]thiophene-2-carboxylate hydrochloride;
2. 4-Methyl-3-[2-(propylamino)-propionamido]-2-thiophenecarboxylic acid, methyl ester hydrochloride

Molecular formula:  $C_{13}H_{21}ClN_2O_3S$  ( $C_{13}H_{20}N_2O_3S \cdot HCl$ )

Molecular weight: 320.84

**Epinephrine Bitartrate:**

Chemical names:

1. 1,2-Benzenediol, 4-[1-hydroxy-2-(methylamino)ethyl]-, (*R*)-, [*R*-(*R*\*,*R*\*)]-2,3-dihydroxybutanedioate (1:1) (salt);
2. (-)-3,4-Dihydroxy- $\alpha$ -[(methylamino)methyl]benzyl alcohol (+)-tartrate (1:1) salt;
3. (-)-1-(3,4-dihydroxyphenyl)-2-methylamino-ethanol (+)- Tartrate

Molecular Formula: Molecular formula:  $C_{13}H_{19}NO_9$  ( $C_9H_{13}NO_3 \cdot C_4H_6O_6$ )

Molecular Weight: 333.3 g/mol (bitartrate salt)

Molecular Weight: 183.2 g/mol (free base)

Chemistry Review Data Sheet

**17. RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Articaine HCl Drug substance	1	Adequate	April 20, 2008	Reviewed by Elsbeth Chikhale, Ph.D.
	II	(b) (4)	Epinephrine Bitartrate Drug substance	3	Adequate	October 14, 2008	Reviewed by Sivakumar Vaithiyalingam, Ph.D.
	II	(b) (4)	Epinephrine free base Drug substance	3	Adequate	November 24, 2008	Reviewed by Bart Ho, Ph.D.
	III	(b) (4)	(b) (4)	7	Adequate	January 30, 2007	Reviewed by Amit Mitra, Ph.D.
						April 25, 2008	Reviewed by Terry Ocheltree, Ph.D.
	III	(b) (4)	(b) (4)	4			

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no relevant revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other: The information for the USP type I glass provided in the DMF amendment dated 4/4/03 was previously reviewed in the two referenced reviews. The specific drawings for the glass cartridges used for this NDA were provided in an amendment to the DMF (dated 10/31/07) but were also provided in the NDA. Other relevant information such as references to 21 CFR and USP tests is also provided in the NDA. Therefore, taken together, a separate DMF review was not deemed necessary.

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

Chemistry Review Data Sheet

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	101,935	Articaine 4% with epinephrine 1:100,000 or 1:200,000 Injection
NDA	20-010	Septocaine® (articaine HCl and epinephrine) Injection 4% and 1:200,000
NDA	20-971	Septocaine® (articaine HCl and epinephrine) Injection 4% and 1:100,000

**18. STATUS:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biowaiver	Biowaiver granted	5/19/09	Patrick Marroum, Ph.D.
Biometrics	N/A		
EES	pending		
Pharm/Tox	Approval	7/31/09	Carlic Huynh, Ph.D.
CDRH	N/A		
Clinical Pharmacology	N/A		
Methods Validation	FDA revalidation is not needed	8/14/09	Elsbeth Chikhale, Ph.D.
DMEPA	pending		
DDMAC	pending		
EA	Categorical exclusion granted (consult not needed)	8/14/09	Elsbeth Chikhale, Ph.D.
Microbiology	pending	8/7/09	Steven Fong, Ph.D.

**19. ORDER OF REVIEW: N/A**

# The Chemistry Review for NDA 22-466

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

From the CMC point of view, the application is APPROVABLE pending an acceptable recommendation from the office of compliance regarding the cGMP status of the manufacturing, testing and packaging facilities. Final labeling will be done in coordination with the clinical division.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

See Microbiology review by Steven Fong, Ph.D.

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product and Drug Substance

##### 1) Drug Product

The proposed drug product is a sterile solution for injection, indicated for local, infiltrative or conductive anesthesia in both simple and complex dental (b) (4) procedures. The route of administration is intra-tissue injection. The proposed commercial drug product is manufactured by Pierrel S.p.A., with manufacturing facilities in Capua, Italy. It is formulated as a sterile aqueous solution for injection with 4% (w/v) articaine hydrochloride, containing either 0.0018% (w/v) or 0.0009% (w/v) epinephrine bitartrate (equivalent to 1:100000 (w/v) and 1:200000 (w/v) concentration of epinephrine as the free base) in USP Type I clear glass cartridges, filled to nominally contain 1.8 mL per cartridge and closed with a (b) (4)

The excipients consist of Sodium Chloride USP; Sodium Metabisulfite NF; Hydrochloric Acid NF; and Water for Injection USP. (b) (4)

This NDA is submitted as a 505(b)2. The reference drug is Septocaine, NDA 22-010 and NDA 20-971. The applicant has requested an in vivo bioavailability/bioequivalence waiver. The biowaiver was granted (see review date 5/19/09 by Patrick Marroum, Ph.D.). The originally proposed storage condition is (b) (4)

(b) (4) and the proposed expiry date is 24 months. The storage statement should be revised to be consistent with the USP room temperature statement (i.e. store below 25 °C (77 °F) with brief excursions permitted between 15 °C and 30 °C (59 °F and 86 °F) (see USP controlled room temperature). The provided stability data support the proposed shelf life of 24 months when stored at room temperature conditions.

## 2) Drug Substance: Articaine HCl:

The drug substance, articaine HCl, is a previously approved drug substance, produced by chemical synthesis. All information regarding the physicochemical properties, impurities, method of synthesis and purification, process controls, control of raw materials, container closure system and stability of articaine HCl are provided in the Drug Master Files (DMFs) (b) (4) held by (b) (4) DMF (b) (4) was reviewed on 4/24/2009 (review #3 by Elsbeth Chikhale, Ph.D.) and found adequate in support of this NDA. Two possibly mutagenic impurities (b) (4) were discussed with the pharmacology/toxicology reviewer and the applicant was asked to justify the levels of these impurities in the drug substance. The applicant has provided a satisfactory response and the levels of these impurities are believed to be safe as indicated by the pharmacology/toxicology review.

## Drug Substance: Epinephrine bitartrate:

The drug substance, epinephrine bitartrate, is a previously approved drug substance, produced by chemical synthesis. All information regarding the physicochemical properties, impurities, method of synthesis and purification, process controls, control of raw materials, container closure system and stability of epinephrine bitartrate are provided in DMFs (b) (4). DMF (b) (4) was reviewed on 10/14/08 (review #13 by Sivakumar Vaithiyalingam, Ph.D.) and found adequate. DMF (b) (4) was reviewed on 11/24/08 (review #1 by Bart Ho, Ph.D.) and found adequate.

## B. Description of How the Drug Product is Intended to be Used

The drug product is indicated for local, infiltrative or conductive anesthesia in both simple and complex dental (b) (4) procedures. The route of administration is intra-tissue injection (submucosal infiltration and/or nerve block). The drug product may be dosed per the following recommended dosages:

Procedure	Volume (mL)	Total dose of articaine HCl (mg)
Infiltration	0.5 – 2.5	20 - 100
Nerve block	0.5 – 3.4	20 - 136
Oral Surgery	1.0 – 5.1	40 - 204

Other volumes may be used provided the following total maximum recommended dose is not exceeded:

- Adults: For normal healthy adults, the maximum dose of articaine HCl administered by submucosal infiltration and/or nerve block should not exceed 7 mg/kg (0.175 mL/kg) or 3.2 mg/lb (0.0795 mL/lb) of body weight, e.g. 7 cartridges (11.9 mL) for a 150 lb. patient.
- Pediatric Patients: Use in pediatric patients under 4 years of age is not recommended. The quantity to be injected should be determined by the age and weight of the child and the magnitude of the operation. (b) (4)  
(b) (4) the maximum dose may be determined by the application of one of the standard pediatric drug formulas. In any case, the maximum dose of 4% articaine HCl should not exceed the equivalent of 7 mg/kg (0.175 mL/kg) or 3.2 mg/lb (0.0795 mL/lb) of body weight.

### C. Basis for Approvability or Not-Approval Recommendation

From the CMC point of view, the application is APPROVABLE pending an acceptable recommendation from the office of compliance regarding the cGMP status of the manufacturing, testing and packaging facilities. Final labeling will be done in coordination with the clinical division.

## III. Administrative

- A. **Reviewer's Signature:** in DARRTS
- B. **Endorsement Block:** in DARRTS
- C. **cc Block:** in DARRTS

42 pages have been withheld in full as B(4)  
CCI/TS immediately following this page

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22466	ORIG 1		ARTICAINE 4% /EPINEPHRINE 1:20000 INJ
NDA 22466	ORIG 1		ARTICAINE 4% /EPINEPHRINE 1:20000 INJ
NDA 22466	ORIG 1		ARTICAINE 4% /EPINEPHRINE 1:20000 INJ

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/s/

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ELSBETH G CHIKHALE  
08/14/2009

ALI H AL HAKIM  
08/14/2009

**NDA 22-466**  
**Trade Name**  
**(articaine HCl and epinephrine bitartrate)**  
**Injection**

**Summary of the Basis for the Recommended Action  
from Chemistry, Manufacturing, and Controls**

**Applicant:** Pierrel S.p.A.

**Indication:** For local, infiltrative or conductive anesthesia in both simple and complex dental (b) (4) procedures.

**Presentation:** The drug product is a sterile aqueous solution for injection formulated with 4% (w/v) articaine hydrochloride, containing either 0.0018% (w/v) or 0.0009% (w/v) epinephrine bitartrate (equivalent to 1:100000 (w/v) and 1:200000 (w/v) concentration of epinephrine as the free base) packaged in USP Type I clear glass cartridges, filled to nominally contain 1.8 mL per cartridge and closed with a (b) (4)

<b>EER Status:</b>	Recommendations:	Withhold
<b>Consults:</b>	EA -	Categorical exclusion provided
	CDRH-	N/A
	Statistics -	N/A
	Methods Validation -	Not recommended
	DMEPA-	Completed
	Biopharm-	N/A
	Microbiology -	Acceptable
	Pharm/toxicology -	N/A

**Original Submission:** 24-November-2008

**Re-submissions:** N/A

**Post-Approval CMC: PMC/PMR:** Microbiolog review indicated that the sponsor will be required to conduct (b) (4) feasibility studies.

**Background:**

This NDA is submitted as a 505(b)(2) application. The reference drug is Septocaine® (articaine hydrochloride and epinephrine bitartrate) Injection; NDA 22-010 (1:200,000 w/v epinephrine) and NDA 20-971 (1:100,000 w/v epinephrine).

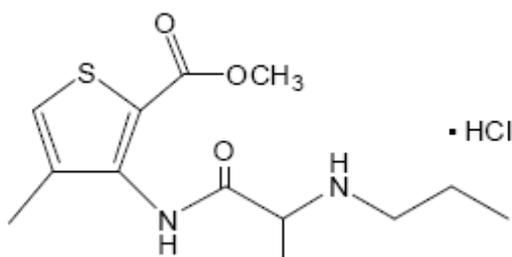
**Drug Substances:****Articaine Hydrochloride:**

The drug substance, Articaine HCl, is a previously approved drug substance, produced by chemical synthesis. All information regarding the physicochemical properties, impurities, method of synthesis and purification, process controls, control of raw materials, container closure system and stability of articaine HCl are provided in the Drug Master File (b) (4) held by (b) (4) DMF (b) (4) was reviewed and found adequate in support of this NDA. However, two possibly mutagenic impurities (b) (4) were discussed with the pharmacology/toxicology reviewer and the applicant was asked to justify the levels of these impurities in the drug substance. The applicant has provided a satisfactory response and the levels of these impurities are believed to be safe as indicated by the pharmacology/ toxicology review.

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

**Articaine hydrochloride:**

**Chemical Name:** Methyl 4-methyl-3-[[ (2RS)-2-(propylamino)propanoyl] amino]thiophene-2-carboxylate hydrochloride;



Molecular formula: C<sub>13</sub>H<sub>21</sub>ClN<sub>2</sub>O<sub>3</sub>S (C<sub>13</sub>H<sub>20</sub>N<sub>2</sub>O<sub>3</sub>S•HCl)

Molecular weight: 320.84

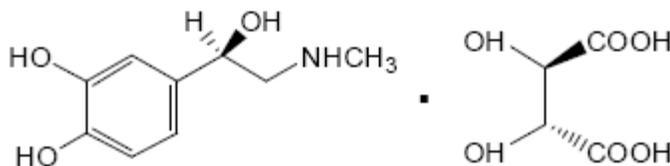
**Epinephrine bitartrate:**

The drug substance, epinephrine bitartrate, is a previously approved drug substance, produced by chemical synthesis. All information regarding the physicochemical properties, impurities, method of synthesis and purification, process controls, control of raw materials, container closure system and stability of epinephrine bitartrate are provided in DMFs (b) (4). Both DMFs were reviewed and found adequate.

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

**Chemical Name:** 1,2-Benzenediol, 4-[1-hydroxy-2-(methylamino)ethyl]-, (R)-, [R-(R\*,R\*)]-2,3-dihydroxybutanedioate (1:1) (salt);

**Structural Formula**



Molecular Formula: Molecular formula:  $C_{13}H_{19}NO_9$  ( $C_9H_{13}NO_3 \cdot C_4H_6O_6$ )

Molecular Weight: 333.3 g/mol (bitartrate salt)

Molecular Weight: 183.2 g/mol (free base)

### Conclusion

The drug substances are satisfactory

### Drug Product:

The proposed drug product is a sterile solution for injection, indicated for local, infiltrative or conductive anesthesia in both simple and complex dental <sup>(b) (4)</sup> procedures. The route of administration is intra-tissue injection. The drug product is formulated as a sterile aqueous solution for injection with 4% (w/v) articaine hydrochloride, containing either 0.0018% (w/v) or 0.0009% (w/v) epinephrine bitartrate (equivalent to 1:100000 (w/v) and 1:200000 (w/v) concentration of epinephrine as the free base) in a single use USP Type I clear glass cartridges, filled to nominally contain 1.8 mL per cartridge and <sup>(b) (4)</sup>

The excipients consist of Sodium Chloride USP; Sodium Metabisulfite NF; Hydrochloric Acid NF; and Water for Injection USP.

The manufacturing process <sup>(b) (4)</sup>

Specifications for the drug product include appearance, identity, pH, volume, assay, related substances, sodium metabisulfite assay, particulates, sterility, and bacterial endotoxins.

**Conclusion:** The drug product is satisfactory.

**Establishment Evaluation Report (EER)**

The cGMP status/overall recommendation for this application is **WITHHOLD**. The cGMP inspection revealed defects and deficiencies related to the integrity of the Microbiological Control aspects of the drug product.

**Overall Conclusion:**

From a CMC perspective, the application is not approvable based on the withhold recommendation from office of compliance with respect to cGMP issues related to the drug product manufacturing site.

Ali Al-Hakim, Ph.D.  
Branch Chief,  
DPA I/ONDQA

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22466	----- ORIG 1	----- PIERREL S.P.A.	----- ARTICAINE 4% /EPINEPHRINE 1:20000 INJ

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/s/

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ALI H AL HAKIM  
09/02/2009

**Initial Quality Assessment**  
**Division of Pre-Marketing Assessment I, Branch II**  
**Office of New Drug Quality Assessment**  
**Division of Anesthesia, Analgesia and Rheumatology Products**

OND Division:	Anesthesia, Analgesia and Rheumatology	
NDA:	22-466	
Applicant:	Pierrel S.p.a.	
Stamp date:	November 25, 2008	
PDUFA Date:	September 25, 2009	
Trademark:	NA	
Established Name:	Articaine HCl with epinephrine bitartrate 4% to 0.002% or 0.001% w/v; 1:100,000 w/v or 1:200,000 w/v	
Dosage Form:	(b) (4) (b) (4)	
Route of Administration:	(b) (4) (b) (4)	
Indication:	Local, infiltrative or conductive anesthesia	
Pharmaceutical Assessment Lead:	Danae D. Christodoulou, Ph.D.	
	YES	NO
ONDQA Fileability:	<u>  √  </u>	<u>      </u>
Comments for 74-Day Letter:	<u>      </u>	<u>  √  </u>

## Summary, Critical Issues and Comments

### A. Summary

The application is filed as a 505(b)(2), non-priority NDA with 10-month review clock, with RLDs Septocaine® Injection (articaine HCl with epinephrine 1:100,000 w/v, NDA 20-971 and 1: 200,000 w/v, NDA 22-010).

The applicant submitted a biowaiver request in M1, Section 1.12.15 with the claim that there are no formulation differences between the RLDs and the Pierrel products that affect bioequivalence. The biowaiver request will be reviewed by ONDQA during this review cycle.

The drug substances, Articaine Hydrochloride Ph.Eur. and Epinephrine Bitartrate USP, are manufactured by (b) (4) located in (b) (4) and (b) (4) located in (b) (4) respectively.

The CMC information is referenced to the corresponding Type II DMFs, (b) (4) for Articaine HCl, (b) (4) for Epinephrine Bitartrate and (b) (4) for epinephrine free base. Letters of Authorization (LoA) have been provided. Note that the epinephrine free base DMF (b) (4) may be cross-referenced from DMF (b) (4) for epinephrine bitartrate and thus LoA is included in the submission. Both drug substances are stable for (b) (4), with stability data referenced to their corresponding DMFs.

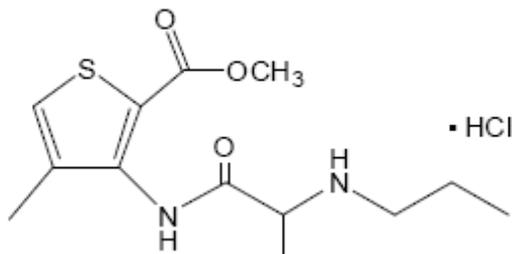
The drug product is formulated as a sterile aqueous solution for injection of 4% (w/v) articaine HCl, containing either 0.002% (w/v) or 0.001% (w/v) epinephrine bitartrate (equivalent to 1:100000 (w/v) and 1:200000 (w/v) concentration of epinephrine as the free base) in USP Type I clear glass cartridges, filled to nominally 1.8 mL per cartridge and closed with a (b) (4).

The excipients consist of Sodium Chloride USP; Sodium Metabisulfite NF; Hydrochloric Acid NF; and Water for Injection USP. Based on real time stability data, a 24 month shelf-life is proposed for the Pierrel products.

### B. Review, Comments and Recommendations

#### Drug Substance Articaine HCl

#### Molecular Structure, Chemical Name, Molecular Formula and Molecular Weight



1. Methyl 4-methyl-3-[[*(2RS)*-2-(propylamino)propanoyl] amino]thiophene-2-carboxylate hydrochloride;
2. 4-Methyl-3-[2-(propylamino)-propionamido]-2-thiophenecarboxylic acid, methyl ester hydrochloride  
Molecular formula: C<sub>13</sub>H<sub>21</sub>ClN<sub>2</sub>O<sub>3</sub>S (C<sub>13</sub>H<sub>20</sub>N<sub>2</sub>O<sub>3</sub>S•HCl)  
Molecular weight: 320.84

As discussed above, articaine HCl is manufactured by (b) (4) (b) (4) and referenced to DMF (b) (4). Specifications are based on the Ph. Eur. monograph for articaine HCl. The names, structures and origins of the structurally related impurities specified in the articaine hydrochloride Ph.Eur. monograph (included in Section 2.3.S.4) are summarized

D. **Comments for 74-day Letter:**

None

- E. **Recommendation for fileability:** The NDA is fileable based on pre-NDA agreements, sufficient number of primary stability batches, and 24 month real stability data at 25°C/60% RH. The NDA is suitable for evaluation and assessment based on FDA and ICH guidelines for submitting CMC information for New Drug Applications.

**Recommendation for Team Review:** The NDA is not recommended for team review. The drug substances are not NMEs, the formulation does not include novel excipients and the manufacturing process for the drug product does not present complexity, e.g., novel delivery or device issues, nor significant development. In addition, the primary stability batches are representative of the commercial process.

**Consults:**

Since the Pierrel products are injectables, microbiology consult is required and was initiated. The application was deemed fileable by the reviewing microbiologist Steven Fong (see filing memorandum in DFS).

Specifications for impurities and leachables/extractables evaluation should be assessed in consultation with the Toxicology reviewer.

The biowaiver request (see DFS) was consulted to Patrick Marroum, biopharmaceutics, ONDQA.

Danae D Christodoulou, Ph.D.  
Pharmaceutical Assessment Lead

1/26/2009  
Date

Ali Al-Hakim, Ph.D.  
Branch II Chief, ONDQA

1/26/2009  
Date

## Fileability Template

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	√		
2	Is the section indexed and paginated adequately?	√		
3	On its face, is the section legible?	√		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full <u>street</u> addresses and CFNs?	√		
5	Is a statement provided that all facilities are ready for GMP inspection?	√		
6	Has an environmental assessment report or categorical exclusion been provided?	√		Categorical exclusion requested 21CFR 25.31(a)
7	Does the section contain controls for the drug substance?	√		
8	Does the section contain controls for the drug product?	√		
9	Has stability data and analysis been provided to support the requested expiration date?	√		Stability data have been provided without statistical analysis
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		Pre-NDA 6/11/2008 IND 101,935
11	Have draft container labels been provided?	√		
12	Has the draft package insert been provided?	√		
13	Has a section been provided on pharmaceutical development/ investigational formulations section?	√		
14	Is there a Methods Validation package?	√		
15	Is a separate microbiological section included?	√		Injectable
16	Have all consults been identified and initiated?	√ N/A N/A N/A N/A √ √		Pharm/Tox Statistics OCP/CDRH/CBER LNC DMETS/ODS Microbiology Biopharmaceutics, ONDQA (Biowaiver)

### Have all DMF References been identified? Yes (√) No ( )

DMF Number	Holder	Description	LoA Included	Status
(b) (4) Type II	(b) (4)	Articaine HCl	Yes	pending
(b) (4) Type II	(b) (4)	Epinephrine Bitartrate	Yes	pending
(b) (4) Type II	(b) (4)	Epinephrine free base	Yes	pending
(b) (4) Type III	(b) (4)	(b) (4)	Yes	pending
(b) (4) Type III	(b) (4)	(b) (4)	Yes	pending

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/s/

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Danae Christodoulou  
1/27/2009 12:08:48 PM  
CHEMIST  
Initial Quality Assessment

Ali Al-Hakim  
1/27/2009 01:42:48 PM  
CHEMIST