

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**22-466**

**MEDICAL REVIEW(S)**



**FDA CENTER FOR DRUG EVALUATION AND RESEARCH**  
**DIVISION OF ANESTHESIA, ANALGESIA, AND RHEUMATOLOGY PRODUCTS**

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Summary Review for Regulatory Action

<b>Date</b>	September 25, 2009
<b>From</b>	Bob A. Rappaport, M.D. Director Division of Anesthesia, Analgesia and Rheumatology Products
<b>Subject</b>	Division Director Summary Review
<b>NDA #</b>	22-466
<b>Applicant Name</b>	Pierrel S.p.A.
<b>Date of Submission</b>	November 25, 2008
<b>PDUFA Goal Date</b>	September 25, 2009
<b>Proprietary Name / Established (USAN) Name</b>	Articaine hydrochloride with epinephrine
<b>Dosage Forms / Strength</b>	Articaine hydrochloride and epinephrine for injection Articaine: 4% (40 mg/mL) 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 [REDACTED] (b) (4) procedures
<b>Action:</b>	Complete Response

<b>Material Reviewed/Consulted</b>	
OND Action Package, including:	
Medical Officer Review	N/A
Statistical Review	N/A.
Pharmacology Toxicology Review	Carlic K. Huynh, Ph.D.; R. Daniel Mellon, Ph.D.
CMC Review	Elsbeth Chikhale, Ph.D.; Ali Al-Hakim, Ph.D.; Patrick Marroum, Ph.D.
Product Quality Microbiology Review	Steven E. Fong, Ph.D.; Stephen E. Langille, Ph.D.
Clinical Pharmacology Review	Srikanth C. Nallani, Ph.D.; Suresh Doddapaneni, Ph.D.
CDTL Review	Bindi Nikhar, M.D.
OSE/DMEPA	Laura Pincock, Pharm.D.; Denise Toyer, Pharm.D.

OND=Office of New Drugs

OSE= Office of Surveillance and Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

DSI=Division of Scientific Investigations

CDTL=Cross-Discipline Team Leader

## 1. Introduction

Pierrel S.p.A. has submitted NDA 22-466 for marketing approval of articaine hydrochloride 4% with epinephrine 1:100,000 and articaine hydrochloride 4% with epinephrine 1:200,000. Both products are injectable solutions indicated for local, infiltrative, or conductive anesthesia in simple and complex dental procedures. The sponsor has submitted this NDA as 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). Articaine hydrochloride is a local anesthetic of the amide class. It differs from other drugs in this class in that it contains a thiophene ring (rather than a (b) (4) which increases its liposolubility. It also contains an ester group which is cleaved by plasma esterases. Articaine was first approved in Europe in 1976. Septocaine was approved for marketing in the U.S. in 2000.

The epinephrine in these products is added to provide vasoconstriction and, thereby, prolong local tissue concentrations of the anesthetic, extending the drug's duration of action. It also acts to reduce the possibility of systemic toxicity related to the rapid absorption of local anesthetic agents. The systemic toxicity of local anesthetics affects primarily the cardiovascular and central nervous system. In addition, these agents can cause methemoglobinemia, particularly in certain subpopulations who are particularly susceptible to this condition. This formulation of articaine also contains sodium metabisulfite which may cause allergic reactions in susceptible individuals. Epinephrine also can cause local or systemic toxicity, including ischemic injury and cardiac arrhythmia.

## 2. Background

At the pre-NDA meeting for this application, the sponsor was informed that the Agency had concerns regarding differences in the product's formulation compared to their referenced drug (RD), Septocaine, which could preclude the submission of a 505(b)(2) application. These differences included:

- NaCl Content: The RD 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 RD products.
- Fill volume: The fill volume of the RD products was 1.7 mL, while the fill volume of the new products was 1.8 mL.

The sponsor was informed that, should they be able to resolve the above concerns with an adequate rationale for why these physiochemical differences were not significant with regard to bioavailability, a waiver of the requirement for a bioavailability study would be possible. They were also informed that no clinical studies would be necessary for their application.

Concerns were raised regarding the sterilization technique for these products. However, in the absence of any concerning findings in the actual microbiological testing, further improvements in sterilization were recommended as a post-marketing commitment.

The Office of Compliance issued an overall withhold recommendation for this application due to deficiencies in microbiological controls found at the product manufacturing site.

## 3. CMC

On review of the application, Dr. Chikhale concluded that the fill volume difference from the RD was acceptable and would have no impact on bioavailability or product quality. The products are manufactured under (b) (4) conditions. They are intended for single-use and contain no preservatives. (b) (4)

(b) (4)

Their study demonstrated that they were able to use temperatures in a range acceptable to the Agency and short-term stability was not significantly impacted. The CMC review team recommends that the sponsor perform a post-marketing study to evaluate a modified (b) (4) cycle per ICH standards. The current products remain stable under normal and accelerated storage conditions supporting a 24-month expiry period.

The sponsor provided data to show that the difference in the NaCl content between their products and the RD products does not significantly impact osmolarity as the relative contribution of the solute ions from NaCl is small. The sponsor also documented that the pH of the RD products, while (b) (4) as per the label at the time of manufacture, drops to (b) (4) in one month or more after the manufacturing date. Thus, the actual pH of the RD products when administered is essentially the same as that of the new products. This resolves the concern raised by Dr. Marroum in his review and the concerns raised by the review team at the pre-NDA meeting regarding the pH adjuster. Dr. Chikhale concurs with the sponsor that these data support the relative bioavailability of the new products to the RD products and, therefore, a relative bioavailability study is not required to support this 505(b)(2) application.

The Office of Compliance issued an overall withhold recommendation after the Pierrel manufacturing site in Italy was inspected. The cGMP inspection revealed multiple defects and deficiencies related to the integrity of the microbiological controls. Dr. Fong, based on these deficiencies, concluded that this application should not be approved at this time. Drs. Chikhale and Al Hakim summarized the requirements to achieve an acceptable level of microbiological control in their memo dated September 24, 2009:

- 1) A detailed description of the procedure used to (b) (4) the (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 (b) (4)  
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.

## 4. Nonclinical Pharmacology/Toxicology

Drs. Huynh and Mellon found that the sponsor had provided adequate characterization of potential leachables and extractables from the container closure system and that there are no novel excipients in the drug product that would suggest safety concerns. There were ten potential impurities identified in the articaine HCl 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, however, (b) (4). QSAR analysis by CDER's 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 do not appear to be degradants, but rather process-related impurities, according to the sponsor;

and the review team agreed with this conclusion. As such, the team has found the application to be acceptable for approval. They recommended post-marketing commitment studies that will attempt to develop improved detection and characterization of [REDACTED] (b) (4).

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

The clinical pharmacology/biopharmaceutics review team found the application to be acceptable for approval. Dr. Marroum noted the following (reproduced from page 15 of Dr. Nikhar's review):

- 1). Differences in NaCl and pH between the two formulations are not thought to have any effect on the bioavailability of the drug in plasma since it is a solution for sub-mucosal injection.
- 2). A bioequivalence study would not be indicative of any difference in uptake of drug into the nerve since the drug concentration is measured at a site far from the local site of action.
- 3). Whether or not clinical safety and efficacy studies are required to assess effects of difference in pH of the two formulations based on differential uptake into the nerve would be a clinical decision.

I agree with Dr. Nikhar who has concluded that, considering that the data from the sponsor's study of the pH of the RD products demonstrated that the pH of the those products is actually the same as the pH of these new formulations at the time the drug would be administered to the patient, there should be no concern regarding differential uptake into the nerve as raised by Dr. Marroum.

## **6. Clinical Microbiology**

Not applicable.

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

No new efficacy data was submitted in support of this application. The sponsor is depending on their 505(b)(2) reference which is acceptable.

## **8. Safety**

No new safety data was generated for this application. Dr. Nikhar has provided a summary of the safety profile of the RD which should be identical to that of these new formulations. She has 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 RD. 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

The review team determined that an advisory committee meeting was unnecessary for this new formulation of articaine/epinephrine as there was no new clinical experience and there were no product concerns that would require the advice of non-Agency experts.

## 10. Pediatrics

This product is exempt from the pediatric study requirements authorized by PREA.

## 11. Other Relevant Regulatory Issues

There are no other outstanding regulatory issues.

## 12. Labeling

Draft changes to the sponsor's proposed label will be appended to the CR Letter.

## 13. Decision/Action/Risk Benefit Assessment

- Regulatory Action  
Complete Response
- Risk Benefit Assessment

The sponsor has demonstrated that these new formulations of articaine and epinephrine are safe and effective when used according to the labeled instructions. They meet the requirements for 505(b)(2) products. However, the Office of Compliance found numerous deficiencies in microbiological controls at the product manufacturing site and issued an overall withhold recommendation for the application; and the ONDQA microbiology reviewer and CMC review team are recommending that the application not be approved until a number of these deficiencies have been adequately addressed. Therefore, I am unable to approve the application at this time.

Both the CMC and pharmacology/toxicology review teams have recommended post-marketing commitment studies. As we are unable to approve the application at this time, the sponsor will be strongly advised to begin these studies as soon as possible, thereby possibly providing results of this work with their resubmission. These studies include:

- (b) (4) feasibility studies

- Study to evaluate the potential for optimizing the sensitivity of the analytical methodology for [REDACTED] (b) (4) in the drug substance
- An in vitro bacterial reverse mutation assay with the isolated [REDACTED] (b) (4)
- An in vitro bacterial reverse mutation assay with the isolated [REDACTED] (b) (4)

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/s/  
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BOB A RAPPAPORT  
09/25/2009

**Cross-Discipline Team Leader Review**  
**NDA # 22-466**  
**Articaine injection**

<b>Date</b>	8/4/2009
<b>From</b>	Bindi Nikhar, MD
<b>Subject</b>	Cross-Discipline Team Leader Memo
<b>NDA#</b>	22-466
<b>Applicant</b>	Pierrel S.p.A.
<b>Date of Submission</b>	11/25/2008
<b>PDUFA Goal Date</b>	9/25/2009
<b>Proprietary Name</b>	To be determined
<b>Established (USAN) names</b>	Articaine hydrochloride w/Epinephrine
<b>Dosage forms/Strength</b>	Articaine hydrochloride 4% (40 mg/ml) w/Epinephrine 1:100,000 (10 mcg/ml) & 1:200,000 (5 mcg/ml) injection (subcutaneous)
<b>Proposed Indication(s)</b>	Local, infiltrative, or conductive anesthesia in both simple and complex dental (b) (4) procedures
<b>Recommended Action</b>	Complete Response

**1. Introduction**

This CDTL memo covers NDA 22-466 for articaine hydrochloride 4% with epinephrine 1:100,000 injection, and articaine hydrochloride 4% with epinephrine 1:200,000 injection, submitted as a 505(b)(2) application by the sponsor, Pierrel S.p.A (Pierrel). The reference listed drugs (RLD) for this application are two formulations of Septocaine injections; NDA 20-971 (articaine with epinephrine at 1:100,000 concentration), and NDA 22-010 (articaine with epinephrine at 1:200,000 concentration). NDA 20-971 was approved on April 3, 2000 and NDA 22-010 was approved on March 30, 2006. The indication sought by the sponsor is identical to the RLD, i.e., local, infiltrative, or conductive anesthesia in simple and complex dental procedures.

There were formulation differences between the RLD and proposed drug product formulations that precluded the application being submitted as an ANDA. However, as discussed later, these differences were minor and at a pre-NDA meeting, the sponsor was advised that it was unlikely that these formulation differences would require the conduct of additional efficacy and safety studies, and that a biowaiver for the conduct of in vivo bioequivalence studies could be requested. The sponsor has not conducted additional clinical studies, has submitted a biowaiver, and is relying on previous Agency's findings of safety and efficacy for both strength articaine formulations.

A primary clinical review has not been written for this NDA; the CDTL memo will address primary and secondary clinical reviews. The memo will cover rationale for the

biowaiver, Pharmtox, Chemistry and Microbiology related issues that arose during review of the NDA as well as an efficacy and safety update since product approval.

## 2. Background

Articaine hydrochloride is a local anesthetic (LA) of the amide class that is widely used in dental practice. Other local anesthetics of the amide class also used in dental practice include prilocaine, lidocaine, mepivacaine, and bupivacaine. Local anesthetics block the generation and conduction of nerve impulses by increasing the threshold for electrical excitation, slowing the propagation of nerve impulses and by reducing the rate of rise of the action potential.

Articaine differs from other amide local anesthetics in that it contains a thiophene ring (instead of a <sup>(b) (4)</sup> of other local anesthetics) which increases its liposolubility, and contains an ester group, hence undergoing biotransformation in the plasma by plasma esterases in addition to its metabolism in the liver. In clinical practice, it is perceived as producing longer duration and increased depth of anesthesia, which may be related to its higher protein binding and lipid solubility. Articaine and its metabolites are excreted by the kidneys.

Articaine was first produced in 1969 when it was known as carticaine; its generic name was changed to articaine when it was introduced in clinical practice in Germany in 1976. Subsequently, its use spread throughout Europe, then to Canada in 1983 and was approved for use in the US in 2000 (Septocaine). Currently, it is widely used in dental practice; as discussed above, its use is preferred because it is perceived to be more successful in achieving anesthesia in various maxillary and mandibular infiltrative procedures and its ability to provide more profound anesthesia.

Epinephrine is a vasoconstrictor that is generally added to dental local anesthetic formulations in ratios between 1: 50,000 and 1: 200,000 to help slow absorption of a LA into the general circulation. Vasoconstrictors help prolong local tissue concentration of a LA thus prolonging duration of action, as well as help avoid systemic toxicity related to rapid absorption of local anesthetics. Sodium metabisulfite is an <sup>(b) (4)</sup> <sup>(b) (4)</sup> <sup>(b) (4)</sup> in these formulations.

Use of local anesthetics, including articaine can be associated with systemic toxicity, typically cardiovascular and central nervous system adverse events, which may arise from accidental intravascular injection, or from higher systemic concentrations. Toxic blood concentrations of articaine can depress cardiac conduction and excitability, which may lead to atrioventricular block, ventricular arrhythmias and cardiac arrest, possibly resulting in fatalities; articaine should be used with caution in patients with heart block. Toxic levels can also cause depression of myocardial contractility as well as peripheral vasodilatation, resulting in decreased cardiac output and arterial blood pressure. CNS adverse events include anxiety, tinnitus, blurred vision, tremors, drowsiness and convulsions. Articaine, in keeping with other local anesthetics is capable of causing

methemoglobinemia; patients with G6-PD deficiency or congenital or idiopathic methemoglobinemia are more susceptible to drug-induced methemoglobinemia. Also, articaine contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms, and life-threatening or less severe asthmatic episodes in certain susceptible people; it is contraindicated in those with a known hypersensitivity to sodium metabisulfite.

Use of epinephrine with local anesthetic solutions can be associated with local or systemic toxicity related to its vasoconstrictor effects. Local toxicity may include ischemic injury or necrosis; systemic toxicity may include cardiac arrhythmias in the presence of general anesthetic agents and an exaggerated vasoconstrictor response in those with peripheral vascular disease and hypertension, and those receiving monoamine oxidase inhibitors, non-selective beta adrenergic antagonists or tricyclic antidepressants. Due to the adrenaline content, articaine formulations containing epinephrine should be used with caution in patients with poorly controlled thyrotoxicosis, untreated hypertension, severe cardiovascular disease and diabetes.

Local anesthetics with or without epinephrine should be used with caution in acutely ill and debilitated patients, and those with predisposing risk factors, such as impaired cardiovascular or hepatic function. Dose reduction is required in pediatric and geriatric patients, and dose adaptation is required for those on concomitant medications such as monoamine reuptake inhibitors, beta blockers, inhalation anesthetics, etc.

**Current labeled dose and indication:**

Indication- Per the current labeled indication, Septocaine (available in pre-filled glass cartridges) is indicated for local, infiltrative or conductive anesthesia in both simple and complex dental procedures. Septocaine with epinephrine 1:100,000 (is preferred over 1:200,000) during operative or complex surgical procedures when improved visualization of the surgical field is desirable.

Per the Septocaine label, upon injection of articaine, the onset of anesthesia is within 1 to 9 minutes of injection and complete anesthesia lasts approximately 1 hour for infiltration and up to 2 hours for nerve block. Also, per the label, administration of Septocaine with epinephrine results in a 3 –to- 5 fold increase in plasma concentrations compared to baseline; however, in healthy adults it does not appear to be associated with marked increases in blood pressure or heart rate, except in the case of accidental intravascular injection.

**Table 1: Recommended Septocaine dosages**

<b>Procedure</b>	<b>Volume (mL)</b>	<b>Total dose of articaine HCl (mg)</b>
Infiltration	0.5-2.5	20-100
Nerve block	0.5-3.4	20-136
Oral surgery	1.0-5.1	40-204

Source: Septocaine label

Table 1 serves as a guide to the amount of anesthetic required for most procedures. Per the label, other volumes may be used, provided the total maximum dose is not exceeded. Maximum recommended dosages are as follows:

- Adult patients: 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; or 7 cartridges (11.9 ml) for a 150 lb patient.
- Pediatric patients: Use in pediatric patients under 4 years of age is not recommended. Quantity to be injected should be determined by age and weight of child and magnitude of the operation. (b) (4)  
(b) (4) 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.

**Proposed dose and indication:**

The sponsor for NDA 22-466 is seeking similar indications and claims as the RLD, Septocaine. Appropriate labeling changes and clarifications will be incorporated into the proposed drug product label (Section 12/Labeling).

**Pre-NDA meeting with sponsor on 6/11/2008**

Following were pertinent points discussed at the Pre-NDA meeting:

**1). Formulation Differences and Route of Submission:**

The Pre-NDA meeting with the sponsor on 6/11/2008 was attended by DAARP, OGD, ORP and ONDQA. The discussion revolved around reasons why the sponsor's product (b) (4) (RLD being Septocaine) and requirements for submitting their proposed drug product (DP) as an NDA via the 505(b)(2) route. There were formulation differences discussed below, between the reference listed drug product and the proposed DP (b) (4).

They were as follows:

- Sodium chloride (NaCl) content – The RLD contained 1.6 mg/ml of NaCl, while the sponsor's proposed DP contained 1.0 mg/ml sodium chloride. 21 CFR 314.94(a)(9)(iii) states that, in general, a generic parenteral product should be Q1/Q2 to the RLD. Exceptions to this requirement included preservatives, buffers and antioxidants, but sodium chloride fell in none of these categories.
- Hydrochloric acid (HCl) - The proposed drug product was to use HCl as a pH adjuster; the RLD used sodium hydroxide (NaOH) for pH adjustment. The Q1/Q2 reasons discussed above would apply.
- Fill volume – There were differences in fill volume between the proposed (1.8 ml) and RLD (1.7 ml) drug products that precluded an (b) (4) application.

(b) (4)

It was also discussed that both articaine formulations with differing epinephrine strengths could be submitted as a single 505(b)(2) application.

## 2). Requirements for NDA Submission:

- The sponsor was advised that no additional nonclinical studies would be required. It was mentioned however that the presence of impurities in the formulation that presented a safety concern would require additional clinical safety or efficacy studies.
- The sponsor was also advised that they could apply for a *waiver of the bioavailability study* together with an appropriate rationale and justification why the differences between the two products would not have an impact on the PK profile of the drug product. The waiver was to take into account the physicochemical differences between the two drug products and explain why they were not significant with regard to bioavailability changes.
- In addition, the sponsor was advised that there appeared to be no need for additional clinical studies, since there was no reason to suggest that the proposed product would perform differently, or have any different risks from the approved product.

The sponsor stated that they would provide a Worldwide Marketing History as well as an efficacy and safety clinical summary, including specific discussion regarding the potential for adverse local tissue reactions.

## 3. CMC

The CMC review was conducted by Dr. Elsbeth Chikhale who indicated that manufacturing processes and controls, process validation and evaluation, control of materials and container closure system were all found satisfactory.

Following were relevant issues:

### 1). Drug substance evaluation:

Both articaine hydrochloride (HCl) and epinephrine are previously approved drug substances.

Articaine HCl- All information regarding its physicochemical properties, method of synthesis, purification, stability and other specifications were found to be adequate. Two process-related mutagenic impurities [REDACTED] <sup>(b) (4)</sup> were identified in the articaine drug substance. Per the CMC reviewer, levels of these impurities were considered safe, and the impurities were not designated as degradants (discussed further in Section 4/Pharmtox).

Epinephrine bitartrate -This is also a previously approved drug substance and all information regarding its physicochemical properties and other specifications were found to be adequate.

## 2). Drug product (DP) evaluation:

### Product description:

The proposed drug product is manufactured by Pierrel S.p.A. under (b) (4) conditions in Italy. It has a target pH of 3.6 and is 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 1:100,000 (w/v), and 1:200,000 (w/v) concentration of epinephrine as the free base}. It is contained in clear glass cartridges filled to 1.8 ml and closed with a (b) (4)

(b) (4) The fill volume difference between the Pierrel (1.8 ml) and RLD products (1.7 ml) was considered by the CMC reviewer to be acceptable.

Excipients include sodium chloride USP (b) (4) sodium metabisulfite USP (b) (4), hydrochloric acid NF (pH adjuster) and water for injection. The CMC reviewer states that all ingredients in the formulation comply with the requirements of the United States Pharmacopoeia (USP)/National formulary (NF). The amounts of articaine HCl, epinephrine and sodium metabisulfite are based on other identical or similar products. The drug product (DP) is formulated with a 10% overage of epinephrine bitartrate (b) (4). Additional measures to mitigate (b) (4) (b) (4) (b) (4) (b) (4)

The proposed storage condition temperature is (b) (4) and proposed expiry date is 24 months. Per the CMC reviewer, the storage conditions for the drug product need to be revised to be consistent with the USP room temperature statement - store below 25<sup>0</sup>C (77<sup>0</sup>F), with brief excursions permitted between 15<sup>0</sup>C and 30<sup>0</sup>C (59<sup>0</sup>F and 86<sup>0</sup>F). The provided stability data support the proposed shelf life of 24 months when stored at room temperature.

### NaCl content:

The proposed DP differs from the RLD (Septocaine) in its sodium chloride content, 1.6 mg/ml versus 1 mg/ml respectively. Per the CMC reviewer, the NaCl content was chosen such that the DP solution is (b) (4). Osmolarity values together with solute data for similar products provided with the NDA showed that the differences in salt concentrations between the two DPs do not significantly affect the osmolarity of the two products because the relative contribution of solute ions from NaCl is relatively small. It was concluded that the sodium chloride content contributed negligibly to overall osmolarity.

**Table 2: Comparative Osmolarity Data for Pierrel and RLD Products**

Product	Measured Osmolarity (mOsM)
Pierrel Articaine with 1:100,000 epinephrine	272.0
Pierrel Articaine with 1:200,000 epinephrine	270.9
Septocaine with 1:100,000 epinephrine	273.5
Septocaine with 1:200,000 epinephrine	271.8

Source: Sponsor submission, Module 2, Volume 1

The CMC reviewer further explained that since osmolarity is a function of dissolved solute concentration, and the composition of the DP formulation is fixed by the required batch charges, the osmolarity will not vary significantly from bath to batch.

**Table 3: Pierrel Articaine Drug Product Unit Composition**

Ingredient	Amount						Function
	Articaine HCl 4% with Epinephrine 1:100,000			Articaine HCl 4% with Epinephrine 1:200,000			
	mg/ml	mg/cartridge	%(w/v)	mg/ml	mg/cartridge	%(w/v)	
Drug substances							
Articaine HCl Ph.Eur.	40	(b) (4)	4	40	(b) (4)	4	Drug substance (local anesthetic)
Epinephrine bitartrate USP*	0.018	(b) (4)	0.0018	0.009	(b) (4)	0.0009	Drug substance (vasoconstrictor)
Excipients:							
Sodium chloride USP	1.0	(b) (4)	(b) (4)	1.0	(b) (4)	(b) (4)	(b) (4)
Sodium metabisulfite NF	0.5	(b) (4)	(b) (4)	0.5	(b) (4)	(b) (4)	(b) (4)
(b) (4) Hydrochloric acid	(b) (4) 3.6 (u) (4)	(b) (4) 3.6 (u) (4)	(b) (4) 3.6 (u) (4)	(b) (4) 3.6 (u) (4)	(b) (4) 3.6 (u) (4)	(b) (4) 3.6 (u) (4)	pH adjustment
Water for injection USP**	q.s.ad	q.s.ad	q.s.ad	q.s.ad	q.s.ad	q.s.ad	Diluent
Total	1mL	1.8mL	100	1mL	1.8 mL	100	
* A 10% overage of epinephrine bitartrate is charged during manufacture to account for (b) (4), and is not included in the quantities listed above. The factor for conversion of epinephrine bitartrate to the free base is (b) (4)							
**Water for injection is (b) (4)							

Source: Sponsor's submission Module 2, Vol. 1.1

pH measurement:

The target pH of the Pierrel drug product is 3.6 versus (b) (4) for the RLD. Epinephrine-containing formulations have a lower pH than those not containing epinephrine, which usually have a pH between about 5.3-5.5 (Table 4). (b) (4)

(b) (4) Per the sponsor, while the original prescribing information for the RLD Septocaine product indicated that the pH was at or near (b) (4), the measured pH of the RLD was about (b) (4). Also, for pH adjustment a base (sodium hydroxide) was used in the RLD formulation, as opposed to an acid (hydrochloric acid) in the Pierrel drug product.

**Table 4: Typical pH of Various Dental Anesthetic Products**

Product Description	Brand Name (Owner)	Typical pH Measured
4% Articaine with epinephrine	Articaine (Pierrel)	3.5-3.6
	Septocaine (Septodont)	(b) (4)
	Alfacaina (Dentsply)	3.5-3.6
	Ultracain (Aventis)	3.5-3.6
	Ubistesin (3M)	3.5-3.6
	Citocartin (Molteni)	3.4-3.5
	Cartidont (Curaden)	3.5-3.6
2% Mepivacaine (with epinephrine)	Carboplyina (Dentsply)	3.5-3.6
	(b) (4)	3.4-3.5
	(b) (4)	3.5-3.6
3% Mepivacaine (no epinephrine)	Carboplyina (Dentsply)	5.3-5.4
	(b) (4)	5.4-5.5
	(b) (4)	5.3-5.4

Source: Sponsor submission, Module 2, Volume 1

To address the inconsistency between the labeled pH (b) (4) of the RLD and measured pH (b) (4) the sponsor conducted a lab scale experiment.

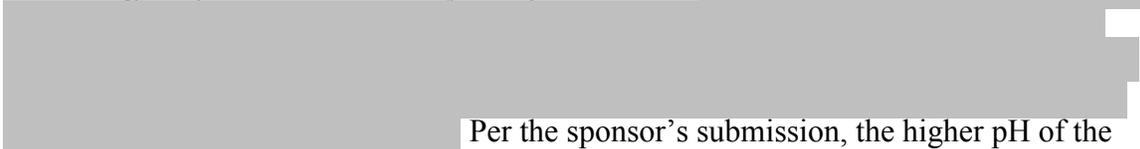


**Table 5: Effect of Storage upon pH of Pierrel and RLD Drug Products**

Articaine with 1:100,000 epinephrine presentation	pH results		
	Initial	(b) (4)	(b) (4)
Pierrel	3.58	(b) (4)	(b) (4)
RLD	(b) (4)	(b) (4)	(b) (4)

Source: Sponsor submission, Module 2, Volume 1

The change in pH was attributed by the sponsor to the (b) (4)



Per the sponsor's submission, the higher pH of the RLD was applicable only initially, prior to additional storage and processing.

During the review process, the sponsor was asked to elaborate further on formulation pH differences. At a telecon held with the sponsor on 3/27/09, the sponsor indicated that their NDA contained stability data that demonstrated that when the DP articaine was

formulated to the initial target pH of the RLD (b) (4), and (b) (4)

The sponsor was asked to procure freshest batches of the RLD, maintain them under controlled storage conditions (25<sup>0</sup>C/60% humidity), and provide data which would show the time frame over which the RLD drug product’s pH dropped such that it was comparable to the Pierrel DP. RLD batch age-based pH information provided by the sponsor demonstrated that the pH of the RLD was (b) (4) by 1 month post-manufacture and that it did not change considerably thereafter, at least until 7 months post-manufacture.

**Table 6: Effect of Batch Age on pH of RLD (Septocaine) Drug Product Formulation**

Data Source	Septocaine Batch Number	Presentation	pH	Batch Age at time of pH measurement (months)
Per March 14, 2009 commitment	710751	1:100,000	(b) (4)	1
	710591	1:200,000		3
Per March 27, 2009 commitment	0195A	1:100,000	3.6	4
	02489	1:100,000		7
	0160A	1:200,000		6

Source: CMC review by Dr. Chikhale

The sponsor explained that the above data demonstrated that for the RLD profound decreases in pH relative to the formulated pH occur very early in the batch lifetime and that this confirms a major decrease in pH (about 1.5 units) during (b) (4) of the RLD originally formulated to a target pH of (b) (4)

The CMC reviewer noted that it is unclear whether this drop in pH is due to effects of (b) (4), or independent of its effects. However, based on data provided by the sponsor, the difference in pH between the Pierrel and RLD products is insignificant after 1 month of manufacture.

**3). Product Quality Microbiology:**

The Product Quality Microbiology review was conducted by Dr. Steven Fong. Following were pertinent issues:

Microbiological attributes of drug product:

Articaine HCl is a sterile drug product (DP), intended for single-use, and containing no preservatives; it may be self-preserving to a certain extent because it has a low pH (~ 3.6) and the active ingredient is an amide. Following formulation, (b) (4)

Studies conducted to assess possible antimicrobial properties of articaine showed that a test species, B. diminuta was unable to survive after 3 hours of product exposure. The bacterial endotoxin limit of the DP was tested and found to conform to established limits.

Microbiological attributes of Container-Closure system and Package Integrity

Microbiological attributes for both were found to be acceptable.

Drug product sterilization/Stability data:

Product sterilization:

(b) (4)

[REDACTED]

The sponsor has agreed to a *post-marketing commitment* that looks into a modified (b) (4) per ICH standards. The sponsor also noted that due to increases in degradant levels, additional overages of epinephrine bitartrate may be required.

Post-Marketing Microbiology commitment:

The sponsor will be required to conduct (b) (4) feasibility studies per a timeline. If these studies demonstrate that short and long term product stability is not adversely affected by appropriate (b) (4) parameters, the sponsor will be required to submit a supplement proposing (b) (4) treatment with these parameters.

Stability data: The drug product remains stable under normal and accelerated storage conditions and supports the proposal for a 24-month storage period.

*Later during the review cycle, the cGMP site inspection conducted in July, 2009 revealed deficiencies related to the integrity of the microbiological control aspects of the drug product discussed below under 'Site Inspection'.*

**Product Microbiology conclusions:**

Based upon review (before results of Office of Compliance site investigation were available), the microbiology reviewer determined that the product quality microbiology assessment of the articaine with epinephrine drug product were overall acceptable and recommended approval. It was noted however that while the (b) (4) processing method of DP sterilization was acceptable, the sponsor will be required to assess the feasibility of (b) (4). The sponsor has agreed to a post-marketing commitment that looks into this; if it is found that (b) (4) has no detrimental effects on short and long-term product stability, the sponsor will be required to incorporate this method of sterilization.

*Please see Dr. Fong's review for further details.*

#### 4). Site inspection

Office of Compliance issued an overall withhold recommendation after the Pierrel site investigation in Italy was conducted from 7/23/2009 – 7/31/2009. The cGMP inspection revealed defects and deficiencies related to the integrity of the microbiological control aspects of the drug product. Form 483 was issued on 7/31/2009. Following observations were cited:

- There were no written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality and purity they purport or are represented to possess. Specifically, validation of sterilization cycles related to the (b) (4) manufacturing process for articaine 4% epinephrine (NDA 22-466) were inadequate.
- There was a failure to thoroughly review any unexplained discrepancy and the failure of a batch or any of its components to meet any of its specifications whether or not the batch had been already distributed.
- The statistical quality control criteria failed to include appropriate acceptance levels and rejection levels.
- (b) (4) processing areas were deficient regarding (b) (4) (b) (4) under positive pressure.
- (u) (4) processing areas were deficient regarding the system for monitoring environmental conditions.
- Equipment used in the manufacture, processing, packing or holding of drug products was not of appropriate design to facilitate operations for its intended use and cleaning and maintenance.
- Laboratory controls did not include the establishment of scientifically sound and appropriate test procedures designed to assure that components, in-process materials and drug products conformed to appropriate standards of identity, strength, quality and purity.

#### CMC conclusions:

Upon review, it was concluded that the difference in osmolarity between the RLD and Pierrel products was insignificant and was not expected to impact safety or efficacy, and that the difference in pH between the two products was insignificant after 1 month of manufacture. However, based on the defects and deficiencies noted on Pierrel site inspection by Office of Compliance for NDA 22-466, the CMC reviewer has recommended a Complete Response action.

Please refer to the CMC review by Dr. Elsbeth Chikhale for further details.

#### 4. Non-Clinical Pharmacology/Toxicology

No new pharmacology or toxicology studies were conducted for this application. Pierrel relied upon the Agency's previous findings of safety for Deproco's Septocaine NDAs (20-971 and 22-010). The Pharmtox reviews (Dr. Carlic Huynh, Pharmtox reviewer, and Dr. Dan Mellon, Pharmtox Supervisor) revolved around process-related drug substance

impurities that were identified as containing structural alerts for mutagenicity, which is discussed below.

### 1). Excipients:

Per the Pharmtox reviewer Dr. Huynh, there are no novel excipients and no concerns regarding current excipients in the drug product formulation. All of the excipients are listed in the IIG database and do not exceed maximum potency limits.

### 2). Extractables and Leachables:

Per Dr. Huynh, extractables testing under harsh conditions such as extraction with (b) (4) but not under physiological conditions, identified various organic compounds, including (b) (4). (b) (4) was found in the cap and plunger using various chemical analytical techniques; however, the leachables testing did not yield the organic compounds (b) (4) identified in the extractables testing (b) (4) is a known carcinogen, however, because of methods of identification of organic compounds discussed above, there are no concerns regarding the extractables/leachables of the proposed articaine drug product. Overall, per Dr. Huynh, the sponsor has provided adequate characterization of potential leachables and extractables from the container closure system. There are no concerns regarding extractables/leachables in the drug product.

### 3). Impurities:

Per Dr. Huynh's review, 10 potential impurities of the articaine HCl drug substance were identified. The majority were not observed at the ICH Q3A(R2) identification level, and (b) (4) was the only impurity observed above the identification level. However, levels of (b) (4) in all drug substance batches were within ICH Q3A(R2) guidelines, and levels of (b) (4) in all drug product batches were within ICH Q3B(R2) guidelines. The analytical detection assay was determined to be sensitive and adequate to detect such impurities in the drug substance.

The Pharmtox reviewer noted two impurities of concern, (b) (4) (b) (4) contains a free amine and (b) (4) (b) (4) both of which contain a structural alert for mutagenicity. QSAR analysis for these two impurities by CDER's ICSAS predicted them as having a low genotoxic potential. (b) (4) were not observed at the ICH Q3A(R2) identification level; according to ICH guidelines, for compounds whose maximum daily dose is  $\leq 2$  g/day, the identification threshold is (b) (4)

It was noted by the Pharmtox reviewer that the levels of (b) (4) were not reported in the drug substance (using state of the art sensitive assays), but that these values were found in their respective DMFs. The LOD for (b) (4) (b) (4) respectively and the LOQ was (b) (4) respectively. Per the RLD label, the maximum daily exposure of a patient to articaine is 7 mg/kg; hence, a normal person weighing 60 kg would be exposed to (b) (4) of articaine on a daily basis. Based on the LOD, daily exposure to (b) (4) would be (b) (4) (b) (4) respectively. Based on the LOQ, daily exposure to (b) (4) would be (b) (4) (b) (4)

(b) (4) respectively. Per the Pharmtox review, this exceeds the specification of NMT (b) (4) for genotoxic or potentially genotoxic residual intermediates.

The sponsor was asked to provide actual levels for both impurities in the drug substance and if present, to include specifications such that the total daily exposure did not exceed (b) (4). The sponsor mentioned that were using currently acceptable state-of-the-art technologies for their detection assays, and (b) (4) have not been detected in drug substance batches. The sponsor also mentioned that that articaine will be administered on an acute basis and that it has been on the market for a number of years with no deleterious side effects reported in literature.

The sponsor further explained that the two impurities were not degradants because (b) (4) (b) (4) to form (b) (4) does not occur as frequently as the (b) (4) to form (b) (4) and there is no source of (b) (4) in the drug product to form (b) (4). This rationale was considered acceptable by the Pharmtox and CMC reviewers and it was concluded that (b) (4) are not degradants in the drug product, and that there is no need to set drug product specifications.

The sponsor has agreed to *post-marketing commitments* that will look into improved detection and characterization of (b) (4). They are as follows:

- Investigate the potential for optimizing the sensitivity of the analytical methodology with regard to (b) (4) and (b) (4) in the DS.
- Conduct an in vitro bacterial reverse mutation assay (Ames assay) with the isolated (b) (4) tested up to the limit dose of the assay
- Conduct an In vitro bacterial reverse mutation assay (Ames assay) with the isolated (b) (4) tested up to the limit dose of the assay.

### **Pharmtox Conclusions:**

NDA 22-466 is acceptable for approval from the Pharmtox perspective. The sponsor has provided adequate characterization of potential leachables and extractables from the container closure system and there are no novel excipients in the drug product that suggest safety concerns. Two theoretical process-related drug substance impurities (b) (4) were identified as containing structural alerts for mutagenicity. While none were detected in the drug substance, the analytical methodology precludes the ability to state that the drug substance levels are below the threshold of toxicological concern of NMT (b) (4). It is possible that in the future there may be improvement in such technology that may permit an analysis of the DS for these impurities. In vitro mutagenicity assays on both impurities should be conducted to verify their mutagenic potential. The Pharmtox team is in agreement with PMCs proposed by the sponsor. No labeling changes are recommended.

Please refer to the Pharmtox review by Dr. Carlic Huynh and the Supervisory Pharmtox memo by Dr. Dan Mellon.

## 5. Clinical Pharmacology/Biopharmaceutics

There was no new clinical pharmacology information submitted for NDA 22-466.

### Clinical Pharmacology review

The Clinical Pharmacology review by Dr. Srikanth Nallani noted the formulation differences between the RLD and Pierrrel drug products and the sponsor's biowaiver request. He concluded that overall, the submitted information is acceptable from a clinical pharmacology perspective.

Please refer to the Clinical Pharmacology review by Dr. Srikanth Nallani for further details.

### Biopharmaceutics review

The Biopharmaceutics review was conducted by Dr. Patrick Marroum/ONDQA. The review revolved around the biowaiver that was discussed at the Pre-NDA meeting on 6/11/2008. Based on the fact that both the proposed DP and the RLD products are almost identical, except a difference in pH and the amount of sodium chloride between the two formulations, the sponsor had requested an in vivo bioequivalence bioavailability waiver.

*Per 21 CFR 320.22(b), for certain drug products, the in vivo bioavailability or bioequivalence of the drug product may be self-evident. FDA shall waive the requirement for the submission of evidence obtained in vivo measuring the bioavailability or demonstrating the bioequivalence of these drug products. A drug product's in vivo bioavailability or bioequivalence may be considered self-evident based on other data in the application if the product meets one of the following criteria:*

*(1) The drug product:*

*(i) Is a parenteral solution intended solely for administration by injection, or an ophthalmic or otic solution; or*

*(ii) Contains the same active and inactive ingredients in the same concentration as the drug product that is the subject of an approved full new drug application or abbreviated new drug application.*

Dr. Marroum discussed the sponsor's contention that the differences in formulation between the proposed (Pierrrel) drug product and the RLD (Septocaine) drug product are unlikely to affect their pharmacokinetic profile and lead to clinical concerns. He noted that the difference in NaCl content between the two formulations did not significantly affect the osmolarity of the two formulations and that the measured drop in pH of the RLD formulation as opposed to the labeled pH was most likely related to effects of (b) (4). These issues have been discussed in Section 3/CMC.

### Biopharmaceutics conclusions:

Dr. Marroum concluded that based on experience with other products, neither the difference in pH, nor the sodium chloride content would have any impact on the bioavailability of articaine and epinephrine in plasma and that the CMC reviewer should determine if the sponsor's justification for drop in RLD pH due to storage and processing

was true (The CMC reviewer has found the sponsor's explanation regarding drop in pH acceptable). He also stated that a bioequivalence study would not determine whether articaine uptake into the nerve (actual site of action) would be different between the two products due to difference in pH, and that whether or not clinical studies are required to assess effects of this difference would be a clinical decision.

The Office of New Drug Quality Assessment *recommended granting an in vivo bioavailability/bioequivalence waiver* based on the following:

- 1). Differences in NaCl and pH between the two formulations are not thought to have any effect on the bioavailability of the drug in plasma since it is a solution for sub-mucosal injection.
- 2). A bioequivalence study would not be indicative of any difference in uptake of drug into the nerve since the drug concentration is measured at a site far from the local site of action.
- 3). Whether or not clinical safety and efficacy studies are required to assess effects of difference in pH of the two formulations based on differential uptake into the nerve would be a clinical decision.

Please refer to Dr. Marroum's review for further details.

## 6. Clinical Microbiology

There were no clinical microbiology review issues for articaine, which is a local anesthetic. Product microbiology issues were addressed in Section 3/CMC.

## 7. Clinical/Statistical - Efficacy

No new clinical safety or efficacy studies were conducted for NDA 22-466. This NDA has been submitted as a 505(b)(2) application with the reference listed drugs being the two Septocaine NDAs (20-971 and 22-010). The proposed indication is similar to the Septocaine NDA (20-971 and 22-010). At the Pre-NDA meeting on 6/11/2008, it had been discussed that due to the relatively minor differences between the RLD and the Pierrel formulations, the sponsor could apply for a biowaiver, which if approved would negate the requirement to conduct clinical safety and efficacy studies for this NDA application. The formulation differences (b) (4)  
(b) (4)

Local anesthetics<sup>1</sup> are poorly soluble in water and are therefore marketed most often as water-soluble hydrochloride (HCl) salts. These HCl salt solutions are acidic (pH 6),

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<sup>1</sup> Pharmacology & Physiology in Anesthetic Practice (3<sup>rd</sup> edition); Robert K. Stoelting; Local Anesthetics, page 158.

which increases the stability<sup>2</sup> of the local anesthetic esters and catecholamines added as vasoconstrictors; as discussed previously, epinephrine is unstable at an alkaline pH. Sodium bisulfite, which is strongly acidic may be added to commercially prepared LA-epinephrine solutions (pH 4) (b) (4)

Differences in pH between the Pierrel and RLD formulations and differences in the labeled vs actual RLD pH measurement were discussed previously in the CMC and Biopharm sections. It was concluded that the pH of the RLD drops within about 1 month after manufacture such that the differences in pH between the Pierrel and RLD products is insignificant after about 1 month of manufacture. A biowaiver has been granted by ONDQA (Please see Dr. Patrick Marroum's review). The clinical concern regarding differences in safety and efficacy between the two formulations is decreased since the two formulations have a pH that is almost equivalent within about 1 month after manufacture. Based on the 505(b)(2) route of approval sought by the sponsor, efficacy information for articaine can be referenced from the RLD Septocaine label; there is no need to perform additional clinical safety and efficacy studies.

The efficacy of articaine as a local anesthetic in dental practice is well defined. The onset of anesthesia is within 1 to 9 minutes of injection, complete anesthesia lasts for approximately 1 hour after infiltrative procedures, and about 2 hours after nerve blocks. Per the Septocaine label, both the 1:100,000 and 1:200,000 epinephrine containing formulations have been studied in previous clinical studies in patients ranging in age from 4 years to 65 years. For most routine dental procedures, the epinephrine 1:200,000 formulation is preferred; however, when more pronounced homeostasis for improved visualization of the surgical field is desirable, the 1:100,000 formulation is used.

The label conveys adequate pediatric (up to 4 years age) and geriatric use information. Dosing information for other clinical situations (concomitant illnesses, acutely ill and debilitated patients, etc) is also well described in the label. The use of articaine in patients with hepatic and renal dysfunction has not been evaluated; however, the label conveys that caution should be used in patients with severe hepatic disease.

Since approval, articaine continues to be widely used as a local anesthetic for dental procedures such as cavity preparation, periodontal surgery or tooth extraction. The sponsor's submission contains a summary of literature reports describing clinical trials conducted since NDA approval. These trials, in pediatric (up to 4 years of age) and adult patients describe comparisons of articaine solutions (using either of the two strengths of epinephrine) with other local anesthetics employed in dental practice. Overall, these literature reports indicate no new significant efficacy information. In current clinical practice, articaine is perceived as being readily able to diffuse through tissues and producing longer duration and profound depth of anesthesia and in general, being fairly effective in various infiltrative and nerve block maxillary and mandibular anesthesia procedures. This may be related to its higher protein binding and lipophilicity properties.

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<sup>2</sup> The Pharmacologic Basis of Therapeutics (11<sup>th</sup> edition); Goodman and Gilman; Local Anesthetics, page 374.

Efficacy conclusions:

The efficacy of articaine is well-defined per the existing Septocaine label. Articaine continues to be used in a wide variety of dental procedures and is perceived as being preferred due to its rapid onset of action, and the depth and duration of anesthesia that it produces. The sponsor did not conduct any additional clinical studies towards NDA 22-466. Based on review of information submitted towards the NDA, there is no need to conduct additional clinical efficacy and safety studies at this time. The label conveys adequate pediatric, geriatric and other special population use information.

## **8. Safety**

The safety of articaine is described in the RLD (Septocaine) label. This information is derived from clinical trials conducted using the articaine with 1: 100,000 and 1:200,000 strength epinephrine solutions. The label also contains information obtained from post-marketing experience. For NDA 22-466, the sponsor supplied an overview of safety and worldwide marketing experience for articaine drug products; a 120-day safety update was also included with their NDA application.

As discussed in Section 2/Background, the cardiovascular and CNS adverse effects of articaine and epinephrine are well known. These are generally associated with higher systemic levels obtained from accidental intravascular injection, or from repeated injection. Cardiovascular adverse events include depression of cardiac conduction and excitability resulting in heart blocks and ventricular arrhythmias, as well as a myocardial depressant effect. CNS adverse events include anxiety, tinnitus, blurred vision, tremors, drowsiness and convulsions. Articaine, in keeping with other local anesthetics is capable of causing methemoglobinemia; patients with G6-PD deficiency or congenital or idiopathic methemoglobinemia are more susceptible to drug-induced methemoglobinemia. Also, articaine contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms, and life-threatening or less severe asthmatic episodes in certain susceptible people; it is contraindicated in those with a known hypersensitivity to sodium metabisulfite.

Use of epinephrine with local anesthetic solutions can be associated with local or systemic toxicity related to its vasoconstrictor effects. Local toxicity may include ischemic injury or necrosis; systemic toxicity may include cardiac arrhythmias in the presence of general anesthetic agents and an exaggerated vasoconstrictor response in those with peripheral vascular disease and hypertension, and those receiving monoamine oxidase inhibitors, non-selective beta adrenergic antagonists or tricyclic antidepressants. Due to the adrenaline content, articaine formulations containing epinephrine should be used with caution in patients with poorly controlled thyrotoxicosis, untreated hypertension, severe cardiovascular diseases and diabetes.

Local anesthetics with or without epinephrine have to be used with caution in patients with predisposing risk factors, such as those with impaired cardiovascular or hepatic function and dose reduction may be required in debilitated and acutely ill patients. Dose

adaptation may be required for those on concomitant medications such as non-selective monoamine reuptake inhibitors, beta blockers, etc.

Per the Septocaine label, articaine is also associated with neurological adverse events such as paresthesia (persistent), hyperesthesia, pain after injection, trismus and facial paralysis. Literature reports indicate that paresthesia continues to be associated with the use of articaine; this is in keeping with the adverse event profile of other local anesthetics such as lidocaine, mepivacaine, prilocaine, bupivacaine, etc.

In addition to salient adverse events described above, the following adverse events are either not fully described in the label or not included, and merit attention:

- Hypoesthesia: Prolonged numbness<sup>3 4</sup> and lip injury<sup>5</sup> related to use of articaine has been described following use of articaine, especially in pediatric age groups; this is most likely related to the longer duration of anesthesia associated with articaine. Literature reports that have described a comparison of articaine and lidocaine<sup>3</sup> in dental practice indicate that although similar in speed and action, articaine is significantly longer lasting when compared to lidocaine. The etiology of this may be greater protein binding of articaine (95%) compared to lidocaine (65%) which results in longer period of sodium channel blockade and longer duration of anesthesia, as well as increased lipophilicity of articaine. A reduced sensation of touch or loss of sensitivity to sensory stimuli can potentially result in tissue injuries, especially soft tissue injuries such as that of the lips and tongue in pediatric age groups. It is recommended that hypoesthesia be added to the Adverse Events section of the label.

- Paralysis of ocular muscles: This has been reported<sup>6</sup> after posterior, superior alveolar injections of articaine during dental anesthesia. Symptoms include diplopia, mydriasis, palpebral ptosis and difficulties in abduction of the affected eye, and have been described as developing immediately after injection of the anesthetic solution and persisting 1 minute to several hours, with generally complete recovery. It has been proposed that local diffusion of the anesthetic solution during dental anesthesia through vascular, lymphatic and nervous networks communicating the pterigomaxillary fossa, through the sphenomaxillary cavity to the orbit may be contributory. Vascular malformations or perivascular trauma from intra-arterial injection or perforation of the vascular wall may be contributory. The literature report also proposed that diffusion of the local anesthetic within the cavernous sinus could have a direct anesthetic effect on the three oculomotor nerves (III, IV and VI). In addition, there may also be sympathetic or parasympathetic involvement with resultant effects; Horner's syndrome like effects (sympathetic involvement) has also been reported as complications. Similar complications, including diplopia and palpebral ptosis have also been described after ophthalmologic surgery

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<sup>3</sup> Comparison of articaine 4% and lidocaine 2% in pediatric age groups; D. Ram & E. Amir; International Journal of Pediatric Dentistry, 2006:16:252-256.

<sup>4</sup> The incidence of adverse reactions following 4% Septocaine in children; Adewumi a, Hall M et al; Pediatric Dentistry, 2008 Sep-Oct; 30(5):424-8.

<sup>5</sup> Articaine hydrochloride: a study of the safety of a new amide local anesthetic; Stanley F. Malamed, Suzanne Gagnon et al; J Am Dent Assoc, Vol 132, No 2, 177-185.

<sup>6</sup> Ophthalmologic complications after intraoral local anesthesia with articaine; M. Penarrocha-Diago, J.M. Sanchis-Bielsa et al; Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 2000 Jul; 90(1):21-4.

related to intraorbital injections, especially in the case of cataract surgery; a myotoxic effect of LA solutions on affected muscles has been attributed in these cases. In the case of dental anesthesia, while such paralysis of ocular muscles has been known to occur after other local anesthetics such as lidocaine and mepivacaine, it is thought that articaine is being increasingly indicted for ophthalmologic complications either because of its increased diffusion through soft tissue and bone, or because of the greater likelihood that articaine caused greater interruption of motor pathways, as well of sensory pathways. It is recommended that paralysis of ocular muscles be added to the Adverse Events section of the label.

- Ischemic injury and necrosis: This is included in the Warnings and Precautions of the label under ‘vasoconstrictor response’ as being related to effect of the vasoconstrictor, epinephrine. A literature report<sup>7</sup> described skin necrosis in a 10 year old girl who received an inferior alveolar nerve block of 4% articaine with 1:200,000 epinephrine on the right side; this was followed by pallor of the right side of the lower lip and chin with subsequent ulceration that healed 15 days later. The skin necrosis was postulated to be due to vascular spasm of the terminal branches of the inferior alveolar artery. While the site of injection, the inferior alveolar nerve was distant from the site of injury, it was postulated that a perivascular injection involving the sympathetic nerves (as regulators of arterial vasoconstriction) might lead to arteriospasm, contributing to the ischemia and necrosis. It is recommended that Ischemic Injury and Necrosis be incorporated in the Adverse Events section of the label.

Based on worldwide marketing experience, the safety profile for articaine is in keeping with its known safety profile. Per the sponsor’s submission, there have been no significant worldwide regulatory actions for articaine drug products.

**Safety conclusions**: Overall, the safety of articaine is in keeping with its known adverse event profile as existing in the labeling for the RLD, Septocaine. It is recommended that the Adverse Events section of the label be augmented as discussed above.

## 9. Advisory Committee Meeting

No Advisory Committee meetings were held for NDA 22-466, that primarily included minor changes in formulation (NaCl content and pH differences) compared to the RLD, Septocaine.

## 10. Pediatrics

No pediatric studies were conducted for this application. The sponsor is requesting a full pediatric waiver stating that the absence of a *new* active ingredient, indication, dosage

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<sup>7</sup> Necrosis of the skin of the chin; Eulalia Torrente-Castells; Jordi Gargallo-Albiol et al; J am Dent assoc, Vol 139, No 12, 1625-1630.

form, dosing regimen or route of administration precludes the requirements for conducting further pediatric assessments.

The RLD label for Septocaine contains adequate safety and efficacy information in pediatric patients up to 4 years of age, which is appropriate since the incidence of pediatric patients < 4 years of age undergoing dental surgical procedures is expected to be low and the use of a local anesthetic for those who do undergo such procedures in the < 4 years age group would be expected to be even lower. Such patients would likely receive general anesthesia as opposed to local anesthesia.

As discussed previously, the sponsor applied for a biowaiver due to changes in formulation between the proposed and RLD formulations which has been granted. The sponsor is not required to conduct further clinical safety and efficacy assessments.

## 11. Other Relevant Regulatory Issues

- Office of Compliance report issued an overall withhold recommendation for NDA 22-466 (discussed in Section 3/CMC).
- There are no unexpired patents for the RLD, Septocaine (articaine HCl with epinephrine 1:100,000 and articaine HCl with epinephrine 1:200,000). There is no unexpired marketing exclusivity for the Septocaine 1:100,000 drug product presentation. The marketing exclusivity for the Septocaine 1:200,000 drug product expired on March 30, 2009.
- DMEPA did not approve the sponsor proposed trade name (b) (4). The sponsor has not yet proposed a new trade name. DMEPA had comments regarding drug product cartridge and container labels which were conveyed to the sponsor.

## 12. Labeling

Sponsor has converted the original RLD Septocaine label to PLR format, including certain formatting changes, which is appropriate. Since NDA 22-466 is a 505(b)(2) application, all relevant CMC, non-clinical, biopharm, clinical and other portions of the label have been imported from the Septocaine label, which is appropriate.

- Per the Microbiology reviewer, the label will have to indicate that the product is indicated for single-use.
- The label incorporates labeling recommendations from the SEALD and DDMAC.
- The label also incorporates recommendations from the Pediatric and Maternal Health team. Recommendations regarding Pregnancy and Lactation sections of the label have been discussed with the Pharmtox team and appropriate revisions

have been made. The Pediatric Use section has been restructured to enhance its clinical usefulness.

- The Warnings and Precautions section of the label have been condensed (Table 7) such that there are 5 categories as opposed to 8 categories conveyed in the Septocaine label.

**Table 7: Recommended changes in Warnings and Precautions Section of the Pierrel Articaine Label (PLR)**

<b>RLD Septocaine label</b>	<b>Proposed Pierrel label</b>
Accidental Intravascular Injection	Accidental Intravascular Injection
Systemic toxicity	Systemic toxicity
Methemoglobinemia	Methemoglobinemia
(b) (4)	Anaphylaxis and allergic-type reactions
Anaphylaxis and allergic-Type reactions	Vasoconstrictor toxicity
Vasoconstrictor response	
(b) (4)	

- It is recommended that the Post-marketing portion of the Adverse Events section of the label be updated to include the following AEs:

- Hypoesthesia
- Paralysis of ocular muscles
- Ischemic injury and necrosis

### 13. Recommendations/Risk Benefit Assessment

NDA 22-466 that includes two formulations of 4% articaine, with epinephrine 1:100,000 and epinephrine 1:200,000 was submitted as a 505(b)(2) application; the RLD being the previously approved Septocaine product that also includes two similar formulations of articaine. No clinical safety or efficacy studies were submitted towards NDA 22-466.

Articaine is a local anesthetic of the amide class that is widely used for dental procedures. It is perceived as having a rapid onset of action, as well as prolonged duration and depth of anesthesia and has lent itself to widespread use in dental anesthesia. Since its approval in the US in 2000 (Septocaine), it continues to be used for local and infiltrative anesthesia as well as dental blocks. Its safety profile is well known overall; the most common adverse effects include cardiovascular and CNS complications associated with all local anesthetics. Its use is also associated with other neurological adverse events such as paresthesia (persistent) and hyperesthesia. Safety update revealed that use of articaine is

also being increasingly associated with hypoesthesia, particularly in pediatric age groups. As discussed previously in Section 8, the label should be updated to include hypoesthesia. Safety review also revealed that use of articaine in intraoral anesthesia can be associated with paralysis of ocular muscles, resulting in symptoms such as diplopia, mydriasis, ptosis and abduction difficulties of the affected eye. These adverse reactions have been reported to resolve without sequelae; however, they are not described in the label and should be included. In addition, it is recommended that ischemic injury and necrosis also be included in the label.

Upon review, it was further determined that two theoretical process-related articaine drug substance impurities (b) (4) were identified as containing structural alerts for mutagenicity. While none were detected in the drug substance batches, the analytical methodology precluded the ability to state that the drug substance levels were below the threshold of toxicological concern. The sponsor has agreed to PMCs that include improvement of detection methods to quantify both impurities in the DS and conduct in vitro mutagenicity assays on both impurities. While detection of these impurities in the articaine drug substance does not necessarily translate into clinical risks given that in general, articaine is used on an acute basis and that it has an extensive, worldwide marketing experience with no reports of mutagenicity at the present time, it is prudent that the sponsor is expected to further clarify this issue.

The proposed drug product differs from the RLD in its NaCL content and pH. Upon review it was determined that the NaCl content differences between the two formulations were not significant enough to produce clinically meaningful differences in terms of safety and efficacy between the two formulations. It was also been determined that while the pH of the RLD was higher than the proposed drug product, this most likely reflected pH before (b) (4) and that by about 1 month post-manufacture, the pH of the RLD decreases, such that it is almost identical to the proposed drug product and stays equivalent at least until 7 months post-manufacture based on data provided by the sponsor. The pH of the Pierrel drug product remains relatively constant and does not drop more than 0.3-0.4 units over the 24-month testing period. Most dental local anesthetic products have a relatively acidic pH, which (b) (4) and hence maintain optimum efficacy and safety.

Based upon discussions at the Pre-NDA meeting, the sponsor did not conduct any additional clinical studies towards NDA 22-466. During the review cycle, the sponsor was granted a waiver of in vivo bioequivalence. The concern regarding pH differences between the RLD and Pierrel formulations translating into clinical significance has been addressed. It is concluded that based on available data regarding the RLD and Pierrel formulations, the difference in pH exists primarily in the immediate period after manufacturing; hence, there would be no difference in pH at the time the drugs are actually administered at the site of action. This addresses Dr. Patrick Marroum's query regarding the need for further clinical studies (discussed in Section 5); the uptake into the nerve of both formulations is expected to be equivalent, negating the need for further clinical safety and efficacy studies for NDA 22-466 at the present time.

The Office of Compliance (OC) site cGMP investigation revealed defects and deficiencies, mostly related to the integrity of the microbiological control aspects of the drug product. While the formal OC review is pending, Form 483 was issued on 7/31/2009 and OC has recommended an overall withhold recommendation for NDA 22-466.

**Conclusions:**

Overall, clinical review of NDA 22-466 showed that use of articaine for local, infiltrative and conductive dental anesthesia since approval in 2000 continues to have a favorable risk-benefit profile. The efficacy of articaine in dental anesthesia is well maintained. Its safety profile is in keeping with other local anesthetics in its class and is well described in the existing Septocaine label. Adverse events such as ocular muscle paralysis and hypoesthesia, not included in the label may be related to the higher protein binding and lipophilicity properties of articaine. These adverse events have also been reported with other local anesthetics, for eg. bupivacaine, xylocaine and will need to be monitored.

The differences in formulations between the RLD and proposed drug products formulations were analyzed during the review cycle and are not expected to translate into clinical significance. However, while formulation differences were resolved, results from the Office of Compliance investigation are very concerning. The cGMP inspection revealed various defects and deficiencies, mostly related to the integrity of the microbiological control aspects of the drug product. These deficiencies may be expected to impact determination of drug sterility, and translate to clinical safety concerns. In conclusion, approval of NDA 22-466 is adversely affected based on risks associated with using a drug product, whose microbiological attributes are not assured.

**Recommendations:**

It is recommended that NDA 22-466 receive a Complete Response. If the NDA is not approved, it is recommended that the Pharmtox and Microbiology post-marketing commitments be conveyed to the sponsor as study agreements that should be completed as soon as possible. There may be additional recommendations for the sponsor based upon final OC review and Product Microbiology re-assessment that takes into account site investigation findings.

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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09/22/2009