

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-466

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

BIOPHARMACEUTICS REVIEW

NDA# 22466
Drug Articaine 4 % with Epinephrine
Formulation Injection
Type Original NDA
Sponsor Pierrel Pharmaceuticals
Letter Date November 24, 2008
Reviewer/Team Leader Patrick Marroum, Ph.D.

Background:

Pierrel Pharmaceuticals is submitting this application to seek approval of a new formulation of Articaine Hydrochloride 4 % with Epinephrine 1:100000 and Articaine Hydrochloride 4 % with Epinephrine 1: 200000 under the provisions of 505 (b)(2) utilizing Septocaine injection as the reference listed drug. The proposed indication is for local, infiltrative or conductive anesthesia in both simple and complex dental (b) (4) procedures.

The sponsor is requesting an in vivo bioequivalence bioavailability waiver based on the fact that the compositions of the 2 products are identical both in terms of active drug but differ in pH and amount of sodium chloride present in the formulation. The table below shows the compositional formula of the Articaine formulation

Components and Composition:

Ingredient	Amount						Function
	Articaine HCl 4% with Epinephrine 1:100000			Articaine HCl 4% with Epinephrine 1:200000			
	mg/mL	mg/cartridge	% (w/v)	mg/mL	mg/cartridge	% (w/v)	
Drug Substances:							
Articaine Hydrochloride 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)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (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	1 mL	1.8 mL	100	1 mL	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)							

TABLE 1

Waiver:

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

This Articaine with Epinephrine injection is not identical to the reference listed drug Septocaine 200 in its composition. However, the sponsor is arguing that the differences in excipients would not affect the pharmacokinetic profile of the product and lead to clinical concerns. The following justifications were provided by the sponsor:

1- Sodium Chloride content: (1.6 mg/ml for the RLD vs 1. mg/ml for Pierrel)
Even though the salt content is different, the Pierrel products are isotonic as can be seen in Table 2 that gives the comparative osmolalities compared to Septocaine 200. According to the sponsor, this is due to the fact that the relative contribution of solute ions from sodium chloride is small.

Product	Measured Osmolarity (mOsM)
Pierrel Articaine with 1:100,000 epinephrine	272.0
Pierrel Articaine with 1:200,000 epinephrine	270.9
Septocaine with 1:100000 epinephrine	273.5
Septocaine with 1:200000 epinephrine	271.8

TABLE 2

2- pH (targeted to ^(b)/₍₄₎ for the RLD vs 3.6 for the Pierrel products)
The sponsor is stating that the formulations containing epinephrine all have very similar pH values between about 3.4-3.6 whereas the formulations without added epinephrine all have very similar pH values between 5.3 and 5.5. This is consistent according to the sponsor with the well known decrease in stability of epinephrine

solutions with increasing pH due to the higher equilibrium concentrations and more (b) (4) of the conjugate free base thus requiring lower pH values when epinephrine is used in the formulation. However, it was found that the measured pH of the RLD was between (b) (4) and not as the stated target of (b) (4). To address this inconsistency between the measured pH and the claimed target pH of the RLD, the sponsor conducted the following laboratory scale experiment. A portion of the bulk drug product containing 4 % Articaine hydrochloride, 1:100000 epinephrine and all other excipients at the proposed commercial concentrations, was prepared except that prior to pH adjustment, (b) (4)

(b) (4)

The results of Table 3 show:

-The pH of the RLD presentation decreased from (b) (4) after (b) (4) (b) (4). The same phenomenon was observed with the Pierrel formulation, the pH decreased from an initial value of 3.58 to a pH of (b) (4)

Table 1.12.15-4. Effect of Storage upon pH of Pierrel and RLD Products		
Articaine with 1:100000 Epinephrine Presentation	pH Results	
	Initial	(b) (4)
Pierrel	3.58	(b) (4)
RLD	(b) (4)	(b) (4)

TABLE 2

This change in pH was attributed by the sponsor to the presence of (b) (4) (b) (4). The (b) (4) is thought to interact with the sodium metabisulfate (b) (4) to produce traces of (b) (4) (b) (4) thus lowering the pH of the formulation.

Therefore, according to the sponsor, the higher pH of the RLD is only applicable initially prior to any additional storage and processing

COMMENTS:

1-The reviewing chemist should determine whether the study that the sponsor conducted to justify the pH difference between the 2 products supports their claim that the pH of the RLD is changing upon storage and processing.

2-Based on experience from other products neither the difference in pH, or sodium chloride content would have any impact on the bioavailability of Articaine and epinephrine in plasma.

3-A bioequivalence study would not answer the question whether Articaine uptake into the nerve (the actual site of action) would be different between the RLD and Articaine due to the difference in pH. This difference in pH on the safety and efficacy should be assessed by the medical division to determine whether additional clinical data would be needed to support the approval of this new formulation.

RECOMMENDATION

The Office of New Drug Quality Assessment has reviewed this submission and recommends granting an in vivo bioavailability/bioequivalence waiver based on the fact that:

1- The differences in formulation in terms of sodium chloride and pH are thought to not to have any effect on the bioavailability of the drug in plasma since it is a solution injected for sub-mucosal administration.

2-The bioequivalence study would not be indicative of any difference in uptake of the drug into the nerve since the drug concentration is measured at a site far from the local site of action.

3-If the pH differences between the 2 products result in different uptake into the nerve, a decision by the clinical division whether additional clinical data is needed to assure the safety and efficacy of this new formulation.

Patrick Marroum, Ph. D.
Office of New Drug Quality Assessment

Date_____

cc: Chikhale

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/s/

Patrick Marroum
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BIOPHARMACEUTICS