during periodontal surgery, 2005), 18 ml of blood was lost during a similar periodontal surgery. Most likely, the method of measuring the blood loss was flawed. The protocol required measurement of all fluids used as irrigation during the surgery and collection of all suctioned fluids. The assumption is that the suctioned fluids are comprised of blood and irrigation fluids, so that the total volume of the suctioned fluids minus the irrigation fluid should leave the volume of blood alone. However, the sponsor did not consider saliva that is generated by the patient during the procedure and included in the suctioned fluids. The method also did not account for swallowed fluid or blood. Assuming that suctioning was well done, little should have been swallowed, but the lack of accountability of the saliva produced most likely results in the overestimation of the blood volume.

The third secondary endpoint, Patient-assessed Level of Anesthesia, was converted by the sponsor into a Summary of Success. This summary of success showed a 100% success rate for subjects in both groups. The sponsor did not explain the transformation of the data into this new outcome, and it is unclear how to interpret the fact that both reached 100% in satisfaction.

4. *What is the likely clinical niche this product may have in a dental practice post-approval?*

Response:
Based upon the results of the studies submitted, there is no advantage of the Septocaine® — compared to the already marketed Septocaine® —. The studies showed equivalent efficacy of the two drugs and a superior visualization with the Septocaine® — However, in practice, dentists use the local anesthetic with the lower concentration of vasoconstrictor as the norm, and the higher concentration of vasoconstrictor for selected procedures, i.e., lengthier procedures for which they prefer that the anesthetic have a greater duration, or in procedures in which reduced bleeding is desirable. Unless the planned dental procedure is to be lengthy, most patients prefer that normal sensation return quickly, which dentists believe will occur with a lower concentration of vasoconstrictor (regardless of the results of this study). Literature also supports the use of lower vasoconstrictor where possible; Trieger says that 1:200,000 is adequate for most procedures.

The American Heart Association has published guidelines in which they recommend that no vasoconstrictor be used in patients with ischemic heart disease unless the elimination of the vasoconstrictor would result in inadequate anesthesia. Although the statement does not specifically discuss use of a lower concentration of epinephrine if a vasoconstrictor is required, most dentists will choose the lower dose. In trials ART-02-001 and ART-02-002, a trend was seen of higher pulse rate after administration of Septocaine® — or Septocaine® —compared to placebo, but no difference could be demonstrated between Septocaine® — and Septocaine® —. It is possible that with a study that was designed to test changes in pulse rate and blood pressure between Septocaine® — and Septocaine® — a significant change could be detected. Regardless of the lack of verified findings, the availability of Septocaine® — will likely

attract dentists who believe that less vasoconstrictor is safer for patients with any cardiovascular risk.

5. *Do you agree with the proposed indication, would you advocate the use of this product for other indications (e.g. tooth cleaning?) Can you foresee off-label uses of this product?*

Response:
As currently proposed, the indication on the sponsor's label includes all aspects of dental treatment that require local anesthesia. The indications on the currently marketed Septocaine, which the sponsor proposes to leave as is on the current label, states "Septocaine is indicated for local, infiltrative, or conductive anesthesia in both simple and complex dental and periodontal procedures. This statement is reasonable as the sponsor has demonstrated that both vasoconstrictor levels of Septocaine are safe and effective for those dental treatments. In terms of the dentist using one of these Septocaines in clinical procedures that are not specifically mentioned, the stated indication categorically includes all treatments that a dentist is licensed and trained to perform. For example, if some individuals require local anesthesia for procedures such as tooth cleaning that do not generally require it, the dentist would use his/her clinical judgment to determine if it is appropriate. Some patients have extremely sensitive teeth, low pain thresholds, or high anxiety levels which do necessitate use of a local anesthetic for even innocuous procedures such as tooth cleaning. The use of the phase "simple and complex dental...procedures" in the indications section already includes tooth cleaning, as it is considered a simple dental procedure.

6. *Would you recommend specific phase 4 studies for this product?*

Response:
Recommendation of phase 4 studies assumes approval, a decision that DDDP cannot provide. As has been discussed in the previous responses, there are shortcomings in the trials that have been conducted and submitted. Although the protocols of the trials fulfilled the needs as relayed by the Agency to the sponsor,

Additional comments:

The challenge if this drug is approved will be to craft a label that provides useful information to the dentist without overstating results or conclusions in a way that may be misleading. The main point to convey in the label concerning the differences between Septocaine® — and Septocaine® — is that Septocaine® — is adequate for the majority of dental procedures. The sponsor demonstrated this by showing non inferiority in efficacy of the Septocaine® — to the Septocaine® —. The only adequately demonstrated indication for Septocaine® — is for procedures where control of bleeding is desired for better visualization. This was demonstrated during Trial ART-02-003 in which the visual field was significantly clearer with the use of Septocaine® — during periodontal surgery. Much care should be taken to avoid a label that implies a better safety profile with the Septocaine® —, or longer duration with the Septocaine® —.

Thank you for allowing the Division of Dermatology and Dental Products to assist you on this matter. Please do not hesitate to contact us with regard to any further questions or comments you may have.

cc: HFD-540/Dental Consult File
HFD-540/DD/Kukich
HFD-540/DTL/Kelsey
HFD-540/PM/Kozma-Fornaro

FDA Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia and Rheumatology Drug Products
HFD-170, White Oak, MD 20857

MEMORANDUM

DATE:	March 22, 2006
TO:	File, NDA 22-010
FROM:	Arthur Simone, M.D., Ph.D. Medical Officer Division of Anesthesia, Analgesia and Rheumatology Products
RE:	Secondary Clinical Review of NDA 22-010, Articaine Hydrochloride 4% with Epinephrine 1:200,000

Background

4% Articaine HCl with epinephrine 1:200,000 (A200) is an amide local anesthetic combined with a vasoconstrictor. 4% Articaine HCl with epinephrine 1:100,000 (A100) was approved as Septocaine® on April 3, 2000 under NDA 20-971 for "local, infiltrative, or conductive anesthesia in both simple and complex dental and periodontal procedures." The 4% articaine HCl with epinephrine 1:100,000 formulation has been registered and approved for use in 53 countries; 4% articaine HCl with epinephrine 1:200,000 formulation has been registered and approved for use in 47 countries, including Canada.

In 1998, the Sponsor, Deproco, Inc., submitted NDA 20-971 seeking approval for both drug formulations: 4% articaine HCl with epinephrine 1:100,000 and 4% articaine HCl with epinephrine 1:200,000. In January 1999, the Agency issued an Approvable letter for both formulations. The requirements for approval were the resolution of two CMC deficiencies (satisfactory approval of the manufacturing facilities and satisfactory resolution of packaging deficiencies) as well as the acceptance of a final printed label. On March 16, 2000, during labeling discussions, the Division noted that all the clinical trials utilized the formulation with epinephrine 1:100,000 and that there were insufficient

data to make findings of safety and efficacy for the formulation containing epinephrine 1:200,000. In addition, there were insufficient data to craft a label which would guide clinicians in determining the appropriate formulation to use for any given patient. The accepted solution was to approve the 4% articaine with epinephrine 1:100,000 formulation and to allow submission of an efficacy supplement seeking approval of 4% articaine with epinephrine 1:200,000 provided a clinically meaningful difference could be found in a direct comparison of the two formulations, thereby providing a basis for product selection. The Approval Letter for Septocaine was issued on April 3, 2000; it included a waiver to assessing the safety and efficacy of the drug in children less than 4 years old.

On September 30, 2005 the Agency received the current submission as an NDA supplement. Because this was a re-submission of a product strength submitted in the original NDA submission, this application was split for administrative purposes and was assigned a new NDA number, NDA 22-010. The original receipt date for NDA 22-010 is considered to be the same as that of NDA 20-971, i.e., March 30, 1998. The Agency deferred the submission of pediatric studies until December 31, 2008 and requested the submission of the pediatric drug development plan within 120 days from the date of the notification, November 23, 2005.

Since the approval of Septocaine, discussions between the Division and the Sponsor regarding the requirements for approving the second formulation resulted in the following items.

1 The studies would have to characterize the pharmacodynamics of A200 and demonstrate its safety.
2 A comparator, only for characterization of the pharmacodynamics, was deemed useful, and instead of 4% prilocaine with epinephrine 1:200,000, the two articaine formulations compared against each other and 4% articaine without epinephrine (Aw/o) was recommended.
3 The required data for A200 were the clinical parameters: onset and duration of effect, anesthesia depth, infiltrative techniques and sites. The patient populations enrolled in the studies could resemble the patient population studied in the original NDA. The purpose of the comparator arm would be to identify background phenomena associated with the drug product, not to seek superiority. Studies on cardiovascular compromised patients were considered unnecessary and inappropriate. One three-arm study using A100, A200 and Aw/o was required. The study was to have appropriate endpoints and be adequately sized for assessing anesthetic properties.
4 Demonstration of a clearer surgical field, i.e., better hemostasis, would be one way of clinically distinguishing the two products.
5 If the pharmacodynamics and pharmacokinetics of the two formulations were found to be similar, the new formulation would have to be demonstrated to be at least as safe as the approved product.

6 A PK/PD animal study or a bioavailability study to assess cardiovascular parameters would be required, or alternatively, a PK/PD study with both formulations in humans could be conducted.

At a teleconference on April 30, 2003, the adequacy of the Sponsor's four proposed protocols were discussed. The key points settled during the teleconference were:

1. The number of patients in the program seemed adequate.
2. The Division asked that — patients be studied at the maximum recommended dose and that a comparison of the local anesthetic absorption of the two formulations be made.
3. The Sponsor was to consider vital sign monitoring as a marker for systemic epinephrine effects and to measure plasma articaine levels.
4. The Sponsor was to incorporate anesthesia efficacy endpoints into the periodontal study (onset, duration and scoring of symptoms).
5. It was deemed acceptable to the Division that a two-arm kinetic study could be employed instead of a three-arm study as in the efficacy studies.

At a teleconference on August 28, 2003, there was further discussion about the proposed studies. The key points of the teleconference were:

1. Studies ART 02-001 and ART 02-002 would be more appropriately powered as non-inferiority trials.
2. The studies might not be able to measure differences between the two formulations, but if the product appeared safe and efficacy could be demonstrated, the Division would consider approval of the second formulation.
3. Local neurotoxicity was to be monitored, although no specific safety measures for neurotoxicity monitoring were discussed.

EFFICACY

Clinical Trials

The Sponsor submitted a clinical program which consisted of three efficacy trials and a pharmacokinetic (PK)-safety study. A total of 182 individuals participated in the studies and were exposed to doses of study drug ranging from 1.0 mL to 11.9 mL.

Study ART 02-001 assessed the anesthetic characteristics of A200, and compared those with A100 and Aw/o. Sixty-three subjects participated and were evaluated with an electric pulp tester (EPT), before and after administration of 1.7 mL of study drug for inferior mandibular block.

Study ART 02-002 had the same study design as ART 02-001. Sixty-three subjects were also enrolled and were evaluated with an EPT, before and after administration of 1.0 mL of study drug by maxillary infiltration.

Study ART 02-003 assessed the hemostatic properties of the epinephrine-containing formulations, A100 and A200, by studying 42 patients who underwent bilateral oral surgery, during which they were exposed to doses ranging from 1.0 to 6.8 mL of each formulation.

Study ART 03-001 was a PK study in which 14 subjects were exposed to 11.9 mL of A100 and A200, one on each of two separate occasions. The Sponsor compared the pharmacokinetic and safety profiles of the two drug products.

The studies are individually described below; each includes discussion of the results and comments on the design, conduct and findings of the trial. Study ART 03-001 is described and discussed in the **SAFETY** section of this review.

Study ART 02-001: "The efficacy and clinical anesthetic characteristics of 4% articaine HCL with 1:200,000 epinephrine, 4% articaine HCL with 1:100,000 epinephrine, and 4% articaine HCL without epinephrine, when administered for inferior alveolar nerve block anesthesia"

This study was a multicenter, randomized, double-blinded, active-control, cross-over trial which sought to demonstrate equivalent anesthetic efficacy between 4% articaine HCL with epinephrine 1:200,000 (A200) and the previously approved 4% articaine HCL with epinephrine 1:100,000 (A100) when used for an inferior alveolar nerve block. In addition, the onset and duration of anesthesia for the two drug products and for the unapproved local anesthetic, 4% articaine without epinephrine (A w/o), were assessed and compared.

Efficacy Endpoints

Primary: success rate for achieving profound anesthesia within 10 minutes of test drug administration

Secondary: comparisons of onset and duration of profound anesthesia for each of the three articaine formulations

Methods

A total of 63 healthy adult volunteers, ages 18-65 years old, with normal pulp vitality of at least one mandibular canine tooth, which was free of gross caries and dental restoration, were randomized to one of six drug sequencing groups. Each group contained a different sequence for administering the test drug products, Aw/o, A100 and A200, with one test drug product administered at each of three clinic visits scheduled one to three weeks apart.

At each visit, baseline Electronic Pulp Testing (EPT) was performed prior to administration of test drug to assess vitality of the tooth. Vitality was defined as the elicitation of a sensation of pulsation, tingling or pain in response to an EPT value of 10-50 units. A mandibular block was then performed on those subjects with normal pulp vitality. A single cartridge (1.7 mL) of test drug was administered over one minute with intermittent aspirations to assess for intravascular injection. EPT testing was performed every 30 seconds following administration of test drug until one of the following occurred.

1. The subject had three consecutive EPT values ≥ 80 within ten minutes following injection of test drug. These subjects were considered to have achieved profound anesthesia; they were labeled as "treatment successes;" and the electronic pulp testing was repeated every five minutes until the profound anesthesia subsided, defined as three consecutive EPT values < 80.
2. The subject failed to have three consecutive EPT values ≥ 80 by ten minutes after injection of test drug. These were considered to not have achieved profound anesthesia and were labeled as "treatment failures." No further EPT assessments were performed on these subjects.

In addition to EPT assessments, subjects rated their sensory function on a 4-category scale:

1. no change or alteration in sensation
2. slight feeling of numbness
3. moderate but not complete feeling of numbness
4. side of mouth is completely numb

Adverse events were assessed during the course of test-drug administration and EPT assessments and at 24 hours following treatment by telephone interview.

Results

The Sponsor reported 18 protocol deviations involving 15 of the 63 enrolled subjects. There were an additional 24 protocol violations reported that ranged from failure to maintain appropriate room temperature to data recording issues. Aside from the protocol violations, there was a single dropout, which was due to withdrawal of consent following the first treatment (A100). The withdrawal was reported by the Sponsor as not due to an adverse event.

The success rates for the treatment groups, the primary efficacy endpoint, were reported as shown in the table below.

Table 1. Profound anesthesia success rates, based on EPT, for the three treatment arms

Treatment Group	% Success based on EPT scoring
Aw/o	25.8
A100	47.6
A200	54.8

The Sponsor reported that there was no difference in the success rates between the two epinephrine-containing formulations, i.e., non-inferiority was demonstrated, but that each epinephrine-containing formulation had a significantly higher success rate than the plain articaine test drug. This contrasted with the subjects' assessments of sensation. The Sponsor indicated that there was no difference in the treatment arms based on subjects who rated the quality of their anesthesia as moderate to complete, which ranged from a 77% in the Aw/o treatment group to 87% in the A100 treatment group; for A200, it was 86%. However, percentages of subjects who reported they felt "completely numb" corresponded much better with EPT-based treatment success rates: 32% had complete numbness with Aw/o, and 40% reported complete numbness with both A100 and A200.

It was noted that EPT-based success rates among study sites differed with the University of Pittsburgh, University of Pennsylvania and Forsythe Institute reporting EPT-based success rates of 69%, 40% and 20%, respectively.

The onset and duration of EPT-assessed profound anesthesia are shown for each treatment arm in the table below, a modified version of Dr. Filie's Table 10.1.1.14.2-1.

Table 2. Onset and duration of anesthesia for each test drug product

Treatment Group	Time to Onset (min.)		Duration of Effect (min.)	
	Mean ± SD	Range	Mean ± SD	Range
Aw/o	4.3 ± 2.5	0.5 - 8.0	49.7 ± 44.2	3.5 - 161.0
A200	4.7 ± 2.6	1.0 - 9.0	51.2 ± 55.9	3.0 - 218.0
A100	4.2 ± 2.8	0.5 - 9.0	61.8 ± 59.0	3.5 - 236.0

Although there were no significant differences in either the onset times or durations of effect for any of the treatment groups, there was a trend for increased duration of effect that corresponded to increased epinephrine content.

Comments

The trial demonstrated, as required by the Division, non-inferiority between the two epinephrine-containing formulations. The Sponsor compared the three articaine products, as requested by the Division. The use of articaine without epinephrine, although an unapproved drug product, provides both assay sensitivity for the EPT testing and support for the addition of epinephrine to the articaine in terms of increasing efficacy as noted by the improved success rates. Comparison of baseline EPT scores with those measured ten minutes after test drug administration was performed to assess efficacy of the three drug products using data from all subjects, both those deemed treatment successes and treatment failures. The data in the table below were provided by Dr. Kim Yongman, the primary statistical reviewer. It shows that each drug product significantly diminished sensation, as assessed by EPT, ten minutes following administration further supporting efficacy. It also suggests a role for epinephrine in enhancing the analgesic effect of articaine.

Table 3. EPT change from baseline at 10 minutes for all subjects in Study ART-02-001

Study Drug	**N**	**EPT Change from baseline Mean (Std. Deviation)**	***p***
Aw/o	62	5.7 (10.5)	<0.0001
A100	63	8.8 (12.9)	<0.0001
A200	62	6.7 (11.3)	<0.0001

The number of protocol deviations and violations were unexpected for a trial of this design and size, but were not considered by the Sponsor or Dr. Filie to have had a significant impact on the study findings. After review of the events, I concur with their assessment.

One concern with the study arises from the differences in success rates that were noted at the different study sites. Not only were the magnitudes of the differences unexpected, but that they also correlated with the level of remuneration the Sponsor provided to the primary investigators. At the time of this review, the Division of Scientific Investigations (DSI) was in the process of assessing the validity of the results from each of the study sites. While the results from this particular trial provide reason for concern, it should be noted that for the two other pivotal trials, the results were similar among the study sites and a correlation between results and investigator remuneration was not observed. In addition, review of the treatment success/failure data by Dr. Filie, did not reveal inconsistencies among the study sites in terms of intra-subject variability of response to

the different test products. Therefore, the findings of the DSI review, still pending at the time of this review, are not critical for the regulatory decision regarding approval of the NDA.

Lastly, there are two concerns related to the findings of this trial. First is the nearly 50% failure rate in achieving profound anesthesia. This could be due, in part, to the inadequacy of EPT for assessing anesthesia; however, its use and the use of the value of 80 units for establishing adequate dental anesthesia are supported by the literature. The EPT findings also correlate well with the subjects' description of how numb they felt, i.e., those who felt completely numb and were treatment "successes" based on EPT scores. An alternative or contributing explanation is that an inadequate dose was used for the trial and that an inadequate amount of time was given for the block to set. According to Dr. Hyman, in his consult, the dose chosen is reasonable for the block performed. The ten minutes allowed for the block to set is also consistent with that required for other local anesthetics in general and the dental anesthetic products in particular. Unfortunately, the ultimate test of efficacy, use during dental procedures, was not assessed; however, use during dental procedures served as the basis for determining efficacy and approving Septocaine. Therefore, assuming the non-inferiority results based on EPT are credible, it would be reasonable to expect similar efficacy for dental procedures.

The second concern related to the trial results is that there is no difference in onset or duration of effect for the two epinephrine-containing formulations. It was hoped that this could serve as one basis for selecting which product to use.

In summary, this trial has demonstrated that A200 is non-inferior to A100 in achieving a level of analgesia suitable for dental procedures and that the two products have similar pharmacodynamics in terms of their onset and duration. It has, in part, satisfied the requirements for approval established by the Division.

Study ART 02-002: "The efficacy and clinical anesthetic characteristics of 4% articaine HCL with 1:200,000 epinephrine, 4% articaine HCL with 1:100,000 epinephrine, and 4% articaine HCL without epinephrine, when administered for maxillary infiltration anesthesia"

This study, which was virtually identical to ART 02-001 except for the dose (1.0 mL instead of 1.7 mL) and site/type of the injection (maxillary infiltration instead of inferior alveolar nerve block), was a multicenter, randomized, double-blinded, active-control, cross-over trial which sought to demonstrate equivalent anesthetic efficacy between 4% articaine with epinephrine 1:200,000 (A200) and the previously approved 4% articaine with epinephrine 1:100,000 (A100) when used for an inferior alveolar nerve block. In addition, the onset and duration of anesthesia for the two drug products and the unapproved local anesthetic, 4% articaine without epinephrine (A w/o), were assessed

and compared.

Efficacy Endpoints

Primary: success rate for achieving profound anesthesia within 10 minutes of test drug administration

Secondary: comparisons of onset and duration of profound anesthesia for each of the three articaine formulations

Methods

A total of 63 healthy adult volunteers, ages 18-65 years old, with normal pulp vitality of the maxillary first premolar tooth on the anesthetized side of the maxilla, or if the maxillary first premolar had been extracted, of the maxillary second premolar, were enrolled. The same tooth was used for the testing at each visit and had to be free of gross caries and dental restoration. Subjects were randomized to one of six drug sequencing groups. Each group contained a different sequence for administering the test drug products, Aw/o, A100 and A200, with one test drug product administered at each of three clinic visits scheduled one to three weeks apart.

At each visit, baseline Electronic Pulp Testing (EPT) was performed prior to administration of test drug to assess vitality of the tooth, defined as an EPT value of 10-50 units for eliciting a sensation of pulsation, tingling or pain. Maxillary infiltration was then performed on those subjects with a normal baseline EPT. A total dose of 1.0 mL of test drug was administered over one minute with intermittent aspirations to assess for intravascular injection. EPT testing was performed every 30 seconds following administration of test drug until one of the following occurred.

1. The subject had three consecutive EPT values ≥ 80 within ten minutes following injection of test drug. These subjects were considered to have achieved profound anesthesia; they were labeled as "treatment successes;" and the electronic pulp testing was repeated every five minutes until the profound anesthesia subsided, defined as three consecutive EPT values < 80.
2. The subject failed to have three consecutive EPT values ≥ 80 by ten minutes after injection of test drug. These were considered to not have achieved profound anesthesia and were labeled as "treatment failures." No further EPT assessments were performed on these subjects.

In addition to EPT assessments, subjects rated their sensory function on a 4-category scale, as was done in ART-02-001:

1. no change or alteration in sensation
2. slight feeling of numbness
3. moderate but not complete feeling of numbness
4. side of mouth is completely numb

Adverse events were assessed during the course of test-drug administration and EPT assessments and at 24 hours following treatment by telephone interview.

Results

The Sponsor reported 47 protocol deviations involving 29 of the 63 enrolled subjects. There were an additional 21 protocol violations reported that ranged from failure to maintain appropriate room temperature to data recording issues - the same as with study ART 02-001. Aside from the protocol violations, there was a single dropout, which was due to withdrawal of consent following the first treatment (A100) - also the same as for study ART 02-001. As with ART 02-001, the withdrawal was reported as not due to an adverse event.

In terms of the primary efficacy endpoint, the success rates for the treatment groups were reported as shown in the table below.

Table 4. Profound anesthesia success rates, based on EPT, for the three treatment arms

Treatment Group	% Success based on EPT scoring
Aw/o	76
A100	95
A200	94

The Sponsor reported that there was no difference in the success rates between the two epinephrine-containing formulations, i.e., non-inferiority was demonstrated, but that each epinephrine-containing formulation had a significantly higher success rate than the plain articaine test drug. The subjects' assessments of sensation following administration of each of the test drug products corresponded to the EPT-based success rates. However, combining the percentages of subjects who reported moderate or complete numbness more closely reflected the EPT-based success rates: 84% for the Aw/o treatment group, 95% for the A100 group and 98% for the A200 group. This differs from the findings in the ART 02-001 trial where only subject reports of complete numbness corresponded to EPT-based success rates.

The success rates among study sites did not differ greatly as they had with study ART 02-001.

The onset and duration of profound anesthesia, as assessed by EPT, are shown for each treatment arm in the table below which is a modified version of Dr. Filie's Table 10.1.2.14.2-1.

Table 5. Onset and duration of anesthesia for each test drug product

Treatment Groups	Time to Onset (min.)		Duration of Effect (min.)	
	Mean ± SD	Range	Mean ± SD	Range
Aw/o	3.0 ± 2.0	0.5 - 9.5	13.3 ± 6.8	2.0 - 38.0
A200	3.1 ± 2.3	0.5 - 9.5	41.6 ± 21.1	3.5 - 103.0
A100	3.0 ± 2.1	0.5 - 9.0	45.0 ± 23.6	5.0 - 99.5

There was no significant difference in the onset time for any of the three test products, nor was there a significant difference in duration of effect for the treatment groups involving the epinephrine-containing formulations. However, the duration of effect for articaine without epinephrine was significantly less than that of both epinephrine-containing products.

Comments

This trial, like ART 02-001, demonstrated non-inferiority between the two epinephrine-containing formulations. As was done with ART 02-001 data, a comparison of baseline EPT scores with those measured ten minutes after test drug administration for all subjects, both those deemed treatment successes and treatment failures, was provided by Dr. Kim Yongman, and summarized in the table below. Once again each drug product significantly diminished sensation. The changes from baseline are greater than those seen in ART 02-001, as were the treatment success rates, suggesting greater efficacy with this method of administration. Thus, these data also support the use of articaine without epinephrine as a comparator as well as a finding of efficacy for each of the epinephrine-containing test drug products.

Table 6. EPT Changes from baseline at 10 minutes for all subjects in Study ART-02-002

Study Drug	N	EPT Change from baseline Mean (Std. Deviation)	*p*
Aw/o	62	16.2 (17.1)	<0.0001
A100	63	20.0 (16.8)	<0.0001
A200	62	22.0 (17.8)	<0.0001

As was the case for ART 02-001, the number of protocol deviations and violations were unexpected for a trial of this design and size, but were not considered by the Sponsor or Dr. Filie to have had a significant impact on the study findings. After review of the events, I concur with their assessment.

In this study, no significant differences in success rates were noted for the different study sites.

The results of this trial, in terms of success rates, were similar to expected rates reported in the literature for maxillary infiltration. In particular, as indicated in Dr. Fred Hyman's consult, the success rate of 95% in the A100 group and 94% in the A200 group are consistent with the > 95% generally cited in the literature. It was noted, however, that subjects' reports of complete numbness did not correspond as well in this trial as they had in ART 02-001. The subjects' assessments indicated success rates, i.e., complete numbness, that were 15% less than the EPT-based success rates for all treatment arms. Although the ultimate test of efficacy, use during dental procedures, was again not assessed, the results of this trial provide additional assurance that efficacy exists. In addition to the above, the magnitude of duration with maxillary infiltration was greater than that for the mandibular block – a finding that is consistent with the literature.

The concern from trial ART 02-001, that there is no difference in duration of effect for the two epinephrine-containing formulations, was reinforced by the results of this trial. However, the increased duration of effect that occurs with the addition of epinephrine, supports the inclusion of the vasoconstrictor in the formulation and provides additional support for the sensitivity of EPT testing for assessing efficacy.

In summary, this trial has also demonstrated that A200 is non-inferior to A100 in achieving a level of analgesia suitable for dental procedures when a 1.0 mL dose is administered by maxillary infiltration. It also demonstrated that the two products have similar pharmacodynamics in terms of onset and duration. These results, in part, satisfy the requirements for approval established by the Division. This trial also provides support for the presence of epinephrine in the formulation.

Study ART 02-003: "A comparison of the hemostatic efficacy of 4% articaine HCl with 1:200,000 epinephrine and 4% articaine HCl with 1:100,000 epinephrine when administered intraorally to induce maxillary anesthesia required for periodontal surgery"

This was a multicenter, randomized, double-blind, active-controlled, cross-over trial which sought to demonstrate the differences in the visualization of the surgical field and surgical blood loss between 4% articaine HCl with 1:200,000 (A200) epinephrine and 4% articaine HCl with 1:100,000 epinephrine (A100). Forty-two patients, ages 21-65 years old, who required bilateral (split-mouth) periodontal surgery of equal complexity were randomized to one of two treatment sequences, so that each patient was exposed to both drugs, one on each side of the mouth on separate surgical sessions. Each patient was allowed to receive up to 4 cartridges (6.8 mL) of anesthetic for maxillary infiltration at each session. At the conclusion of the procedure, the surgeon rated the clearness of the surgical field with two different scales, the patient assessed the level of their anesthesia, and the blood loss during the procedures was measured.

Efficacy Endpoints

Primary: visualization of the surgical field as rated by the surgeon using a 7-category scale

Secondary: surgeon's expectation of blood loss as rated by a 7-category scale
comparison of measured blood loss
hemostatic success rate
patients' assessments of their anesthetic using a 4-category scale

Methods

Enrolled patients underwent matched bilateral surgeries performed during two visits scheduled 3-5 weeks apart. The surgeries were gingival flap procedures and were matched on the basis of the number of teeth involved and level of attachment loss. The study drug was injected immediately prior to surgery, and the injection volume was determined by the site and extent of the surgical procedure. A maximum of four cartridges of anesthetic (6.8 mL) was permitted. Topical anesthetic ([redacted]) was applied to the mucosa prior to all anesthetic injections. Conduct of the second procedure was the same as the first with the exception that the alternative study drug was used.

Surgical blood loss was determined from the time of the initial incision to the time the final suture was placed. All blood, saliva and irrigation solutions were collected. The volume of all irrigation solutions used was recorded. All gauze was pre-weighed, and the gauze that was used during the procedure was collected immediately after removal from the mouth and weighed. The sponsor indicated that the saliva collected should not vary with the amount of epinephrine used, and therefore, the total difference in weight between the materials collected for each surgery should reflect a difference in blood loss.

The table below is modified from one in Dr. Fred Hyman's review and summarizes the scales used to assess efficacy in this trial.

Table 7. Features of scales used to assess hemostatic and anesthetic efficacy

Feature	Scale		
	The Visualization of Surgical Field Scale	**The Expectation of Blood Loss Scale**	**Patient-assessed Level of Anesthesia**
When measured	Conclusion of each of the surgical procedures	Conclusion of each of the surgical procedures	Immediately prior to injection, immediately prior to surgery, and following placement of the final suture
Question Posed	"How clear was your visualization of the surgical field?"	"Based on your past experience performing periodontal surgery, how well did the local anesthetic limit bleeding?"	Select one of the following categories to describe your anesthesia
Question Posed To:	Surgeon	Surgeon	Subject
Choice of Responses	1) Very unclear	1) Much worse than expected	1) Normal sensation
	2) Moderately unclear	2) Moderately worse than expected	2) Slight feeling of numbness
	3) Slightly unclear	3) Slightly worse than expected	3) Moderate but not complete feeling of numbness
	4) Neither clear nor unclear	4) Equal to expected	4) Side of my mouth is completely numb
	5) Slightly clear	5) Slightly better than expected	
	6) Moderately clear	6) Moderately better than expected	
	7) Very clear	7) Much better than expected	

Hemostatic success was determined on the basis of whether, at any time during the surgical procedure, the surgeon felt that the surgical field was very unclear or bleeding was considered much worse than expected, and therefore, an alternative anesthetic, i.e., one cartridge of 2% lidocaine hydrochloride with 1:50,000 epinephrine, needed to be administered. Failure was, therefore, defined as the decision that an alternative anesthetic agent was required to allow adequate visualization of the surgical field.

Results

There were 19 protocol violations involving 16 patients. None were likely to have affected the outcome of the trial in a significant fashion.

Combining the surgeons' ratings of the visual field that included slightly, moderately and very clear, the Sponsor compared the findings for the two study drugs. In all, there were

35/42 incidents of clear ratings (83%) for A100 and 25/42 such incidents (60%) for A200. The difference was significant ($p = 0.03$).

A similar analysis was conducted for the surgeons' expectations of blood loss with incidents of blood loss that ranged from equal-to-expected to much-better-than-expected combined for the comparison of the two test products. There were 36/42 such reports (86%) for A100 and 30/42 reports (72%) for the A200. This difference was also significant ($p = 0.03$).

There was a substantial difference in measured blood loss between the two formulations as well, despite the wide ranges noted throughout the trial. The mean (standard deviation) blood loss for A100 was 55 mL (36 mL); for A200, it was 70 mL (53 mL). The differences were significant ($p = 0.02$).

The Sponsor reported a hemostasis success rate of 100% for both formulations since none of the surgeons had to use lidocaine with epinephrine to control bleeding, despite ratings of "very unclear" (n=1) and "moderately unclear" (n=4) for the A200 formulation.

The patients' assessments of their anesthetic indicated that 98% felt moderately or completely numb with A100 and 100% felt the same with A200 prior to their surgery. At the end of surgery, 81% of the A100 group and 76% of the A200 group reported the same level of numbness.

Comments

Although none of the scales used in this study were validated (validated metrics for the same parameters do not yet exist), the results they provided yield rather convincing evidence that A100 was superior to A200 at minimizing bloody obstruction of the surgical field. The difference in blood loss associated with the two formulations substantiates the finding. Dr. Filie, in her review, further refined the analyses done by the Sponsor. Because the scales used by the surgeons were subjective and the categories not precisely defined, e.g., the difference between a slightly unclear, neither clear nor unclear, and slightly clear surgical fields was not specified, Dr. Filie compared the formulations using only the extreme positive outcomes. Taking into consideration only the ratings of "moderately clear" and "very clear" for visualization of the surgical fields, A100 with 26/42 (62%) positive ratings was superior to A200 which had 20/42 (48%) positive ratings. This result, like that for the Sponsor's analysis, was statistically significant ($p = 0.046$). A similar comparison for the surgeons' expectation of blood loss yielded a different result. Comparing findings of "moderately better than expected" and "much better than expected" combined resulted in 13/42 occurrences (31%) for A100 and 11/42 occurrences (26%) for A200. While the trend was in the correct direction, i.e., a better outcome with A100, the difference was not significant. As this was a secondary endpoint, a trend in the proper direction is adequate to support the claim.

Lastly, the patients' assessments of sensation suggest an adequate level of analgesia with both drug products. The need for additional dosing with test drug for purposes of providing greater analgesia was not assessed; however, dosing within the confines of the protocol appears to have been sufficient for the procedures performed.

Summary of Findings for Efficacy

The Sponsor has satisfied the requirements imposed by the Division for the types of trials that needed to be conducted and succeeded in demonstrating the following:

1. A200 is not inferior to A100 in producing anesthesia when administered for inferior alveolar nerve block using a 1.7 mL volume of drug product.
2. A200 is not inferior to A100 in producing anesthesia when administered by maxillary infiltration using a 1.0 mL volume of drug product.
3. Use of A100 provides better surgical field visualization and less blood loss than A200 when used for maxillary periodontal surgery.
4. Onset and duration of action for A100 and A200 are similar when administered for inferior alveolar nerve block and maxillary infiltration.

Not addressed in these trials were methods to deal with treatment failures. This is a particular concern for inferior alveolar nerve blocks where the average success rate was 55% for A200. Whether repeat dosing or waiting longer than ten minutes for the block to set increases efficacy was not evaluated. Use of alternative local anesthetic agents to deal with a failed articaine block was also not evaluated.

SAFETY

Clinical Trials

Study ART 03-001 was specifically designed to assess and compare cardiovascular safety of A100 and A200. The three efficacy trials also included safety assessments. Study ART 03-001 is described and discussed in detail below; the safety assessments made in the other trials are summarized below that.

Study ART-03-001: "Peak plasma articaine concentrations and cardiovascular responses following intraoral administration of 4% articaine HCl with 1:200,000 epinephrine and 4% articaine HCl with 1:100,000 epinephrine"

This randomized, double-blind, active-controlled, single-site, pharmacokinetic (PK) study was designed to also evaluate the differences in cardiovascular effects between 4% articaine HCl with 1:100,000 epinephrine (A100) and 4% articaine HCl with 1:200,000 epinephrine (A200). Fourteen healthy adults, ages 21-65 years old, were exposed to 11.9 mL of both A100 and A200 with only one product administered at each of two treatment sessions. The subjects underwent multiple blood draws for PK analysis as well as cardiovascular assessments using an acoustic tonometer and blood pressure monitoring.

Objectives

Primary:

- Evaluate differences in peak articaine plasma concentrations (C_{max}) following administration of the maximum recommended doses of A100 and A200
- Evaluate differences in cardiovascular parameters related to the administration of the maximum recommended doses of A100 and A200

Secondary:

- The time to peak plasma concentrations of articaine
- Subject's rating of anesthetic efficacy.

Methods

Subjects were randomly assigned to receive either A100 or A200 at the first session followed by treatment with the alternative product one to three weeks later. At each treatment, blood samples were collected at baseline (T_0), immediately prior to the local anesthetic injections, and at 8, 10, 15, 20, 25, 30, 40, 50, 60, 90 and 120 minutes following administration of the first cartridge to determine plasma concentrations of articaine.

The maximum dose of articaine was selected to simulate clinical situations where seven

cartridges of anesthetic would be required, e.g., four third-molar extractions, and to assess plasma concentrations of anesthetic with different concentrations of epinephrine. The anesthetic volume, used for both treatment arms, was 7 cartridges (11.9 mL) - the maximum recommended dose for 4% articaine with epinephrine 1:100,000 for a 70 kg adult.

At time T_0, seven cartridges of study drug were to be administered sequentially to the following sites: one cartridge for right maxillary infiltration of the first molar; one cartridge for left maxillary infiltration of the first molar; one cartridge for right maxillary first premolar infiltration; one cartridge for left maxillary first premolar infiltration; one cartridge for right inferior alveolar nerve block; one cartridge for left inferior alveolar nerve block; one-half cartridge for right mandibular buccal -infiltration; and one-half cartridge for left mandibular buccal infiltration. Each full-cartridge injection was to be administered over one minute; each half-cartridge injection was to be administered over 30 seconds. Injections were administered in the same order for all treatments and were given with frequent aspirations to test for intravascular injection. One dentist provided all of the injections for a given subject. A topical anesthetic ([redacted]) was applied to injection sites prior to administration.

For each study session, an acoustic tonometer was fitted over the radial artery of one arm and an automated blood pressure monitor was placed on the opposite arm. According to the Sponsor, cardiovascular measurements obtained through this non-invasive method, tonometry, correlate closely with invasive measures of heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), estimated cardiac output (CO), large artery elasticity index (C1), small artery elasticity index (C2), and systemic vascular resistance (SVR). The Sponsor indicated that the device has demonstrated differences not only in blood pressure recordings but also in large and small artery compliance between hypertensive and normotensive individuals and between those that had and had not experience major cardiovascular events, e.g., stroke, myocardial infarction and coronary bypass grafting. The cardiovascular measures of HR, SBP, DBP, MBP, SV, CO, Cl, C2 and SVR were determined at baseline, immediately prior to administration of the anesthetic injections, and every 10 minutes after initiation of the injections, i.e., pre-dose, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110 and 120 minutes after time T_0. The maximum change from baseline for each parameter was determined for each subject at each session.

A descriptive report of anesthetic characteristics was simultaneously elicited. At baseline and following blood sampling, subjects were asked to select one of the following four categories of sensory function:

1) normal sensation
2) slight feeling of numbness
3) moderate but not complete feeling of numbness
4) my mouth is completely numb.

Results

Fourteen patients were enrolled and randomized. One did not complete the study due to consent withdrawal (subject received only A100 treatment). The reason for withdrawal was not indicated, but was noted not to be due to an adverse event. Twelve subjects were included in the PK analyses; the remaining subject was missing multiple blood samples and, therefore, was excluded by the Sponsor from the PK analyses, but not the safety analyses. According to the final study report, there were 22 protocol deviations affecting data for 10 subjects. Seven deviations were related to lack of blood draws secondary to loss of IV access, three involved blood samples collected in wrong tubes, and seven were missed cardiovascular measurements; the remaining five deviations were minor and not expected to affect the outcomes.

The table below summarizes the key PK findings of this study. The Sponsor indicated there were no significant differences between test drugs for any of the PK parameters evaluated.

Table 8. PK findings for Study ART 03-001

Parameter	A100	A200
C_{max}	1960 ng/mL	2060 ng/mL
T_{max}	0.36 hr	0.37 hr
$T_{1/2}$	0.73 hr	0.74 hr

The maximum changes from baseline for each of the hemodynamic parameters were compared for the two treatment groups. The table below summarizes the changes and treatment differences.

Table 9. Treatment differences for maximum changes of hemodynamic parameters

Parameter	Change from Baseline Mean (SD)		Treatment Difference	*p*
	A100	A200		
Pulse (b/min)	2 (18)	-3 (11)	5	0.03
Diastolic Blood Pressure (mmHg)	-8 (8)	-5 (7)	3	0.27
Systolic Blood Pressure (mmHg)	-5 (14)	-5 (16)	0	0.92
Mean Arterial Blood Pressure (mmHg)	-6 (9)	-4 (9)	2	0.48
Cardiac Output (L/min)	-0.1 (1)	0.1 (1)	0.2	0.69

The results for stroke volume, large and small artery elasticity, and systemic vascular resistance were similar to those of blood pressure and cardiac output, i.e., the changes were small and did not rise to the level of statistical significance. The Sponsor noted that there was a significant difference ($p = 0.04$) in pretreatment systolic blood pressures

[mean (SD)] between treatment groups: A100: 127 mmHg (7); A200: 121 mmHg (8). The Sponsor also noted that at 10 minutes post-treatment, there were significant differences between treatment groups for systolic blood pressure [A100: 131 mmHg and A200: 125 mmHg ($p = 0.046$)] and for cardiac output [A100: 6.4 L/min; A200: 6.2 L/min ($p = 0.045$)].

The subjects' assessments of their level of numbness indicated that by 10 minutes following the administration of the first cartridge of test drug, 6/13 (46%) of those who received A100 experienced complete numbness compared to 8/13 (62%) of those who received A200; the difference was not significant ($p = 0.41$). By 120 minutes after injection of the first cartridge of test drug, 12/13 (92%) of subjects in both treatment arms had experienced complete numbness. Whether the numbness occurred at all or only some of the injection sites was not evaluated.

Comments
The PK findings indicate similar profiles for the two articaine formulations and suggest the pharmacologic effects of the two drug products should also be similar. The hemodynamic measurements indicate the two products behave in a similar fashion. Although the Sponsor reported statistically significant differences in some hemodynamic parameters between the formulations, accounting for multiplicity would preclude any of the differences from being considered statistically significant. None of the differences rise to the level of clinical significance. There is no evidence that the differences observed confer either a safety benefit to patients or a basis for distinguishing when to use each of the two products.

The clinical significance of the subjects' assessments of their level of numbness is that 10 minutes may not be a sufficient waiting period for either A100 or A200 to exert its full effect and that waiting may be as useful as injecting additional drug product to achieve the desired level of analgesia.

ART 02-001
Immediately following the procedure, the following adverse events were specifically assessed:

- unexpected pain upon injection
- positive aspiration during injection
- discomfort at the injection site
- swelling at the site of injection (hematoma)
- rash or other abnormal skin reaction
- syncope

Follow-up consisted of an interview by phone call approximately 24 hours after injection of study drug. Vital signs were recorded at baseline, and every five minutes for the entire EPT session.

ART 02-002

Immediately following the procedure, the following adverse events were specifically assessed:

- unexpected pain upon injection
- positive aspiration during injection
- discomfort at the injection site
- swelling at the site of injection (hematoma)
- rash or other abnormal skin reaction
- syncope

Follow-up consisted of an interview by phone call approximately 24 hours after injection of study drug. Vital signs were recorded at baseline, 10 minutes after administration of the study drug, and at the end of the treatment session.

ART 02-003

Safety assessments made during this trial included the following:

- unexpected pain upon injection
- positive aspiration during injection
- discomfort at the injection site
- swelling at the sit of injection
- rash or abnormal skin reaction
- syncope

Vital signs were assessed prior to injection, 10 minutes following injection and at the conclusion the session. Seven days following surgery, subjects returned for a post-op visit; during that visit, subjects were specifically asked about swelling, headache, pain, infection, gingivitis, numbness or tingling, excessive bleeding, and poor healing.

Integrated Review of Safety

Dr. Filie has provided an extensive review of the safety data. Sections of her review are summarized below.

Extent and Duration of Exposure

A total of 182 subjects were enrolled in the four clinical trials. All subjects received at least one 1-mL dose of A100; 179 of those subjects also received at least one 1-mL dose of A200. In addition, 124 of the enrolled subjects also received at least one 1-mL dose of the articaine 4% test drug product that contained no epinephrine, Aw/o. The table below is based on Dr. Filie's review table, 7.2.1-1, and shows the breakdown of drug product exposures for each study.

Table 10. Articaine exposures for submitted studies.

Trial	Formulation			Doses (mL)
	A100 (N)	A200 (N)	Aw/o (N)	
ART02-001	63	62	62	1.7
ART02-002	63	62	62	1.0
ART02-003	42	42	0	1.0-6.8
ART03-001	14	13	0	11.9
Total	*182*	*179*	*124*	

Deaths

No deaths occurred following treatment with any of the articaine test-drug products in any of the clinical trials.

Serious Adverse Events

There were no non-fatal serious adverse events (SAEs) in clinical trials in either the ISS or the 120-Day Safety update.

Discontinuations Due to Adverse Events

The Sponsor reported that there were no discontinuations due to adverse events.

Adverse Events

Those adverse events that occurred with a frequency of $\geq 1\%$ for either the A100 or A200 formulation were listed in Table 7.1.5.4-1 on page 40 of Dr. Filie's review and are presented below with minor modifications. None of the adverse events reported for trials ART 02-001, ART 02-002 and ART 03-001 lasted more than 24 hours, i.e., they resolved by the time of the follow-up telephone interview. Similarly, the adverse events for ART 02-003 had fully resolved by the follow-up visit, which occurred 7 days following study drug administration. None of the adverse events recorded were serious in nature, none were severe in intensity, and none resulted in subject discontinuation.

Table 11. Adverse events occurring with a frequency ≥ 1% for A100 and A200

Adverse Event	A100 (N= 182)	A200 (N=179)
Pain	14 (7.6%)	11 (6.1%)
Headache	6 (3.2%)	9 (5.0%)
Positive blood aspiration during injection	6 (3.2%)	3 (1.6%)
Swelling	5 (2.7%)	3 (1.6%)
Trismus	3 (1.6%)	1 (0.5%)
Nausea and emesis	0 (0%)	3 (1.6%)
Sleepiness	1 (0.5%)	2 (1.1%)
Numbness and tingling	2 (1.0%)	1 (0.5%)
Palpitation	2 (1.0%)	0 (0%)
Ear symptoms (earache, otitis media)	2 (1.0%)	1 (0.5%)
Cough, persistent cough	2 (1.0%)	0 (0%)

Laboratory Results and Electrocardiograms

No laboratory evaluations or electrocardiograms were performed following test drug administration in any of the trials included in this submission.

Adverse Experiences Not From Clinical Trials

In his consult, Dr. Fred Hyman states that the literature has remarked upon a concern with articaine's ability to create paresthesias, particularly in the mandibular nerve following mandibular block injection. It has been hypothesized that nerve irritation is greater when local anesthetic agents with higher concentrations (e.g., 4% articaine vs. 2% lidocaine) are used. As an example, Dr. Hyman cites a 20-year Canadian study in which data on all of the dental local anesthetics used in Ontario were collected. These included 2% lidocaine, 2% etidocaine, 2% mepivacaine, 4% prilocaine, and 4% articaine. The highest incidence of paresthesia occurred after the administration of 4% articaine and 4% prilocaine. Based upon the local anesthetic use figures in Ontario, the incidences of these events was much higher than expected only in these two local agents. Additional evidence supporting a role for concentration on nerve irritation is that prilocaine is available in 3% and 4% concentrations in European countries where the reported incidence of paresthesia is significantly greater for the 4% formulation than for the 3% formulation. Although no persistent paresthesias were reported in the studies for the current submission, the number of subjects enrolled was insufficient to assess this relatively rare outcome.

Dr. Filie, in conjunction with Martin Pollock, Ph.D., from the Office of Drug Safety (ODS), conducted a review of the Adverse Event Reporting System (AERS) database for adverse events reported with Septocaine since its approval. They found multiple cases of events related to or suggestive of nerve injury including paresthesias and hypoesthesia. A formal consult from ODS was pending at the time of this review; however, the findings from the AERS data search were consistent with the adverse events already listed in the

Septocaine label where they were stated to occur in less than one percent of subjects. It should be possible to appropriately label the A200 product with the information currently available, and modify it, if necessary, when the ODS consult is complete.

Dosing

Dose finding studies were not conducted for this drug product. Such information would have been useful, particularly in providing guidance to clinicians who find themselves dealing with a failed inferior alveolar nerve block. In study ART 02-001, approximately half the subjects had inadequate anesthesia, based on EPT results, following a single dose of articaine products containing epinephrine. The study did not assess whether the anesthesia was adequate for any procedures, nor did it assess whether waiting longer or administering additional doses of anesthetic would rectify the problem. Studies ART 02-003 and ART 03-001 suggest there are no safety risks associated with additional dosing; improved efficacy, however, was not assessed. The need to deal with failed maxillary infiltration is likely to occur less often based on the EPT findings of ART 02-002, but this too was not adequately dealt with in the submission. The safety of repeat dosing at a single site was not evaluated although such dosing may have occurred in ART 02-003.

Special Populations

Special populations were not studied in any of the trials included with this submission. All subjects were healthy adults ages 18 to 65 years old.

Summary of Findings for Safety

Evaluations of safety for the submission were limited to assessments of hemodynamic parameters and monitoring for adverse events. Such evaluations are appropriate for the drug product and the indication sought. The duration of assessment was adequate. A shortcoming in the hemodynamic monitoring was noted, i.e., the times at which assessments were made would preclude the detection of intravascular injection of the drug product. Such injection would likely subject a patient to the systemic effects of epinephrine, e.g., increased heart rate and blood pressure, which would occur within seconds after the injection and resolve within a minute or two. Only continuous monitoring would detect the occurrence of such an event, but this was not utilized in the trials conducted. Concern for the lack of such monitoring is mitigated by the previous finding of safety for A100 which contains twice the amount of epinephrine as A200. Safety findings for the submission, for both A100 and A200, include the following.

1. No serious or severe adverse events occurred during the studies submitted.
2. Adverse events reported in the studies conducted were consistent with those observed in the trials submitted for the approval of Septocaine and reported in the package insert.
3. All adverse events reported resolved over the course of one to seven days following drug administration.

4. Administration of maximum recommended doses to healthy adults resulted in hemodynamic changes that were not of clinical significance.
5. There were no clinically significant differences between the two epinephrine-containing formulations in terms of hemodynamic parameters following administration.

FINDINGS FROM OTHER DISCIPLINES

Chemistry, Manufacturing and Controls

At the time of this review, Drs. Ravi Harapanhalli and William Adams were awaiting additional information from the Sponsor, and therefore, they had not completed their review. An inspection of an alternative manufacturing facility is also pending at the time of this review.

Nonclinical Pharmacology and Toxicology

Drs. Mamata De and R. Daniel Mellon have reviewed the non-clinical information submitted with this application and noted that it consisted of two articles published since the submission of the Septocaine NDA. Doğan et al.[1] described the effects of articaine on wound healing and described incidents of tissue necrosis with and lower breaking-strength test results for articaine versus lidocaine. The authors, however, went on to describe articaine as a safe local anesthetic agent for head and neck surgery. The reviewers note that tissue toxicity due to local anesthetic agents has been reported to be greater when a vasoconstrictor is also injected due to the prolonged local exposure to the anesthetic drug. As the current product has less epinephrine than the currently approved articaine product, and several other dental local anesthetic products, and as there have not been reports of delayed wound healing or tissue necrosis with the approved articaine product, Drs. De and Mellon indicated that A200 should pose minimal risk in these regards and that risk is not likely to be clinically relevant. I concur with their conclusions.

The second paper, by Ribeiro et al.,[2] reported on a rat study of tissue reactions related to subcutaneous injection of normal saline, 0.5% bupivacaine with epinephrine 1:200,000, 4% articaine with epinephrine 1:100,000, 2% lidocaine without a vasoconstrictor, or mepivacaine with epinephrine 1:100,000 at the site of a surgical incision. The authors reported that the bupivacaine group presented the most intense inflammatory reaction; the articaine and mepivacaine groups generated similar inflammatory reactions; and the lidocaine group presented the least intense inflammatory reaction. In addition, areas of necrosis were observed in two tissue samples of the articaine group; no other groups had this finding. It was speculated by Dr. Mellon that clinical significance of these findings relative to the A200 formulation are minimal. He indicated that if there have been no reports of tissue necrosis with the approved formulation and the A200 formulation has half the epinephrine of A100 thereby further reducing the risk of perfusion-related necrosis, the clinical relevance of the rat findings are minimal. I concur with his arguments.

Clinical Pharmacology and Biopharmaceutics

Drs. Srikanth Nallani and Suresh Doddapaneni commented in their review that the rate and extent of systemic absorption in terms of T_{max}, Cmax and AUC of articaine after the administration of A100 and A 200 are similar, and therefore, both strengths are expected to have similar systemic pharmacologic effects. I concur with their findings.

CONCLUSIONS

Executive Summary

The Sponsor has demonstrated analgesic efficacy of 4% articaine hydrochloride with epinephrine 1:200,000 (A200) in two active-control trials in which it was found to be non-inferior to the previously approved Septocaine® (NDA 20-971), which has 4% articaine with epinephrine 1:100,000. These trials also demonstrated greater efficacy of the two epinephrine-containing products compared to 4% articaine hydrochloride without epinephrine for achieving a level of analgesia, as measured by EPT, considered suitable for performing certain dental procedures. As assessed by maxillary infiltration and inferior alveolar nerve block, there was no significant difference between the two epinephrine-containing formulations in either the onset or the duration of anesthesia. There was also no meaningful difference between the two products in terms of hemodynamic responses. An additional trial compared blood loss associated with the two epinephrine-containing products when used in patients undergoing bilateral periodontal surgery. Based on the dentists' assessment of the surgical field and blood loss measurements, Septocaine provided significantly better visualization of the field than A200, a not unanticipated result. Repeat dosing in an effort to compensate for a failed block was not assessed.

Recommendations

Based on the data submitted the Sponsor, a recommendation for Approval is made provided the pending CMC issues are satisfied and the product label reflects the following information regarding the two 4% articaine hydrochloride with epinephrine products:

1. Neither product should be used if there is a patient-safety concern over the use of an epinephrine-containing drug product.
2. The two articaine with epinephrine formulations provide similar anesthesia for most dental procedures.
3. If obstruction of the surgical field by blood is a concern or hemostasis is otherwise important to the procedure, 4% articaine hydrochloride with epinephrine 1:100,000 should be selected over 4% articaine hydrochloride with epinephrine 1:200,000.
4. Rescue from a failed anesthetic for either maxillary infiltration or inferior alveolar nerve block has not been evaluated with repeat dosing of 4% articaine with epinephrine or of other dental anesthetic products.

In addition to the above, it is recommended that the Sponsor should be encouraged to evaluate safety and efficacy of the two 4% articaine with epinephrine products in pediatric patients ages 2-16 years old.

References

[1] Doğan N, Űçok C, Korkmaz C, Űçok Ő and Karasu Ha; (2003) The Effects of Articaine Hydrochloride On Wound Healing: An Experimental Study. J. Oral Maillofac. Surg. 61:1467-1470.

[2] Ribeiro, P.P., Jr., Sanches, M.G. and Okamoto, T; (2003) Comparative Analysis of Tissue Reactions to Anesthetic Solutions: Histological Analysis in Subcutaneous Tissue of Rats. Anesth. Prog. 50:169-180.

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/s/

Arthur Simone
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MEDICAL OFFICER

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FDA Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia and Rheumatology Drug Products
HFD-170, White Oak, MD 20857

MEMORANDUM

DATE: March 30, 2006

TO: File, NDA 22-010

FROM: Arthur Simone, M.D., Ph.D.
Medical Officer
Division of Anesthesia, Analgesia and
Rheumatology Products

RE: Addendum to Secondary Clinical Review of NDA 22-010,
Articaine Hydrochloride 4% with Epinephrine 1:200,000

One of the recommendations included in the Office of Drug Safety consultation for the labeling of 4% Articaine Hydrochloride with Epinephrine 1:200,000 was insertion of the underlined wording shown below that constitutes the first bullet point in the **Information for Patients** section.

"The patient should be informed in advance of the possibility of temporary loss of sensation and muscle function following infiltration and nerve block injections

This wording and its location presents several clinical concerns:

1. The wording is accurate but does not reflect that
2. The mentioning to patients of this complication for this product and not for the other vasoconstrictor-containing local anesthetics used in dentistry could suggest to them that there is less risk if a different agent is selected. There is no evidence on which to base such a decision.

3. The inclusion of this serious risk and not others in the points of information that should be discussed prior to the administration of the medication could also lead [redacted] convulsions, that may occur and which may occur with similar frequency.

4 [redacted]

Following discussion of the above with Fred Hyman, D.D.S., and his concurrence that inclusion of the suggested wording may be more of a hindrance than a help to clinicians, I recommend that this language not be included in this section of the label.

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/s/

Arthur Simone
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