CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-010

PROPRIETARY NAME REVIEW(S)

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; White Oak 22, Mail Stop 4447)

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HFD-170

THROUGH: Alina Mahmud, RPh, MS, Team Leader
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FROM: Felicia Duffy, RN, BSN, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

PRODUCT NAME: **Septocaine®** — (Articaine HCl 4% with Epinephrine 1:200,000) Injection **NDA #**: 22-010	**SPONSOR:** Deproco

RECOMMENDATIONS:

1. DMETS does not recommend the use of the proprietary name, Septocaine — based on modifier concerns. We recommend the sponsor refer to 2% Xylocaine as an example on how to define Septocaine — because it is also a combination injectable local dental anesthetic with the same characteristics as Septocaine —.

2. DMETS recommends implementation of the label and labeling recommendations outlined in Section III of this review to minimize potential errors with the use of this product.

3. DDMAC finds the proprietary name Septocaine — acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, project manager, at 301-796-5038.

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; WO22; Mail Stop 4447
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: December 29, 2005

NDA#: 22-010

NAME OF DRUG: Septocaine® — (Articaine 4% with Epinephrine 1:200,000) Injection

NDA HOLDER: Deproco

I. INTRODUCTION:

This consult was written in response to a request from the Division of Anesthesia, Analgesia, and Rheumatology Products (HFD-170) for assessment of the proprietary name, "Septocaine —", regarding potential name confusion with other proprietary or established drug names. Container labels, carton and insert labeling were provided for review and comment.

Septocaine (NDA 20-971) was approved on April 3, 2000. The currently marketed Septocaine contains Articaine 4% with Epinephrine 1:100,000. The proposed drug product, Septocaine —, contains Articaine 4% with Epinephrine 1:200,000. After discussion with the Division Project Manager, it was clarified that if Septocaine — is approved, the sponsor proposes to rename the current product, Septocaine, as Septocaine —. Thus, the prospective products to be marketed are Septocaine — and Septocaine —.

PRODUCT INFORMATION

Septocaine — is indicated for local, infiltrative, or conductive anesthesia in both simple and complex dental and periodontal procedures. Septocaine — is preferred when it is desirable to limit exposure to cardiovascular stresses from the higher doses of epinephrine contained in Septocaine/Septocaine —. It will be administered by submucosal infiltration and/or nerve block. The maximum recommended dosage for adults and children over 4 years is 7 mg/kg. Septocaine — will be available in 1.7 mL glass cartridges in boxes of 50 cartridges.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to Septocaine — to a degree where potential confusion between drug names could occur under the usual clinical practice settings. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

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[1] MICROMEDEX Integrated Index, 2005, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-05, and the electronic online version of the FDA Orange Book.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Septocaine —. Potential concerns regarding drug marketing and promotion related to the proposed name(s) were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name Septocaine —, acceptable from a promotional perspective.

2. The Expert Panel identified one proprietary name that was thought to have the potential for confusion with Septocaine — This product is listed in Table 1 (see below), along with the dosage forms available and usual dosage.

3. The Expert Panel also had the following comments on the use of "—" as a modifier.

   a. The modifier — is misleading. It makes it seem as if there is only one active ingredient when there are actually two.

   b. Numeric modifiers can be confusing especially when the modifier doesn't exactly match what it's supposed to modify (e.g., — vs. 200,000) in the case of Septocaine —. The number could be misconstrued as a dose with the units missing, e.g. — (ml) or — (mg). Additionally, modifiers are often left off, which may cause even more confusion. For example, a prescriber orders Septocaine, leaves off the modifier, and the pharmacist is not aware that there are now two different products available. The potential exists for the wrong product strength to be dispensed.

   c. The modifier can create difficulty in naming future products. If the sponsor plans to market a 5% product with epinephrine 1:100,000, what would they name it? Septocaine 5/100?

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Septocaine —	Articaine HCl 4% with Epinephrine 1:200,000 Injection	0.5 mL to 5.4 mL (20 mg to 204 mg of Articaine) by submucosal infiltration and/or nerve block.	
Septocaine	Articaine HCl 4% with Epinephrine 1:100,000 Injection	0.5 mL to 5.4 mL (20 mg to 204 mg of Articaine) by submucosal infiltration and/or nerve block.	LA/SA
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Septocaine — were discussed by the Expert Panel (EPD).

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Septocaine — with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 122 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. Requisition prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Septocaine — (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Requisition 1 RX:	Septocaine — Dispense two 1.7 mL vials
Requisition 2 RX:	

2. Results:

The written and verbal prescriptions were sent out with the incorrect modifier (—). The correct modifier is "—)". However, all of the respondents in the written prescription studies omitted the modifier. Thus, DMETS did not resubmit the study since the modifier did not effect the study outcome. See Appendix A for the complete listing of interpretations from the verbal and written studies.

D. ADVERSE EVENT REPORTING SYSTEM (AERS)

Since the root name "Septocaine" is currently marketed, DMETS searched the FDA Adverse Event Reporting System (AERS) database for any post-marketing medication error reports related to Septocaine. The MedDRA Higher Level Group Term (HLGT), "Medication Errors", and the verbatim substance name "Septoc%" were used to perform the AERS search. This search retrieved one case where an oral maxillary surgeon indicated that the packaging of Septocaine and Carbocaine 3% look similar due to the colors of the ring around the dental carpule. The reporter noted that the gold ring for Septocaine looked similar to the beige ring for Carbocaine. However, these colors are approved by the American Dental Association (ADA) as part of color coding for local anesthetic cartridges. A second case was retrieved but pertained to an adverse event of chronic pain after receiving Septocaine.

E. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name, Septocaine —), the primary concerns related to the use of the modifier ' —)". Additionally, DMETS had concerns with the potential for look-alike and sound-alike confusion with Septocaine —and Septocaine. DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was confirmation that Septocaine — could be confused with Septocaine as all of the respondents from the written prescription studies omitted the modifier and interpreted the proposed name as Septocaine. Although there are limitations to the predictive value of these studies, primarily due to the sample size, we have acquired safety concerns due to positive interpretation with this drug product. A positive finding in a study with a small sample size may indicate a high risk and potential for medication errors when extrapolated to the general U.S. population.

1. Sound-alike/Look-alike Names

DMETS is concerned with confusion between Septocaine and Septocaine —. DMETS envisions confusion and error in the event the modifier is inadvertently omitted. Omission of a modifier is cited in the literature as a common cause of medication errors[4]. The modifier may be omitted due to a lack of awareness that two Septocaine products exist. This confusion may be even more likely if a pharmacy stocks only one of the two drugs at the time of product launch and is unaware of the new product. To further confuse matter, both drugs share an overlapping route of administration (submucosal infiltration), indication for use (anesthesia for dental procedures), overlapping ingredient (articaine), articaine strength (4%), usual dosage, setting (dental setting), and dosage form (injection). In addition, Septocaine and Septocaine —, will be stored next to each other on dental clinic shelves, increasing the risk of selection and dispensing errors. Thus, in the event that Septocaine — is approved, it will be extremely important to differentiate the Septocaine and Septocaine — labels and labeling in order to avoid shelf selection errors. DMETS also recommends that educational measures be taken to emphasize the differences between these two medications at the time of product launch.

2. Modifier Concerns

DMETS believes the modifier "— ' is misleading and as a result may cause confusion. The modifier is misleading because Septocaine — is a combination product containing articaine with epinephrine, however, the modifier " — does not make reference to the strength of the primary active ingredient (articaine). The modifier " —" refers only to the epinephrine component. Thus, this naming convention may lead healthcare providers to believe that the product only contains one active ingredient. Secondly, the use of the modifier " — ' does not clearly represent the strength of epinephrine (1:200,000). We recognize the sponsor proposes to change the name "Septocaine" from Septocaine to Septocaine — if Septocaine — is approved. However, Septocaine — may be misinterpreted as having a higher concentration of epinephrine than Septocaine —. When in reality, Septocaine —contains the same concentration of articaine with a higher concentration of epinephrine (1:100,000) compared to Septocaine —. This may be significant if the goal is to limit exposure to cardiovascular stresses from the higher doses of epinephrine contained in Septocaine —).

Additionally, it was noted by the Expert Panel that a numeric modifier can cause confusion for practitioners because there are no units associated with the number (e.g., mg, mL, etc.). Thus, a practitioner may think that the number represents the number of doses, the strength, or volume. Upon consideration, DMETS believes that the use of a numeric modifier without reference to a unit of measure may be used safely in this context given the characteristics of this drug product. As noted above, the modifier "—does not accurately reflect the combination product and should be revised. An Expert Panel member

[4] Lesar TS. Prescribing Errors Involving Medication Dosage Forms. *J Gen Intern Med.* 2002; 17(8): 579-587.

questioned how the sponsor would name the drug product if the Articaine per-cent was changed. For example, if the sponsor plans to market a 5% product with epinephrine 1:100,000, what would they name it? Septocaine 5/100? Thus, the numeric modifier can also create difficulty in naming future products.

DMETS recommends the sponsor use a similar naming convention used for the dental product Xylocaine with epinephrine. The product is named 2% Xylocaine with epinephrine 1:50,000 and 2% Xylocaine with epinephrine 1:100,000. Additionally, the labels and labeling of the product are in accordance with the ADA anesthesia color codes. The product name for 2% Xylocaine with epinephrine 1:50,000 appears on a green background and the 2% Xylocaine with epinephrine 1:100,000 appears on a red background. DMETS believes that the naming convention used for the drug product is the most accurate representation of the medication and we have not had any reported cases of name confusion with this naming convention.

III. COMMENTS TO THE SPONSOR:

DMETS does not recommend the use of the proprietary name, Septocaine — based in safety concerns. In reviewing the proprietary name, the primary concerns related to the modifier.

DMETS believes the modifier " —' is misleading and as a result may cause confusion. The modifier is misleading because Septocaine — is a combination product containing articaine with epinephrine, however, the modifier " —" does not make reference to the strength of the primary active ingredient (articaine). The modifier " — refers only to the epinephrine component. Thus, this naming convention may lead healthcare providers to believe that the product only contains one active ingredient. Secondly, the use of the modifier " — ' does not clearly represent the strength of epinephrine (1:200,000). We recognize the sponsor proposes to change the name "Septocaine" from Septocaine to Septocaine — if Septocaine — is approved. However, Septocaine —, may be misinterpreted as having a higher concentration of epinephrine than Septocaine —. When in reality, Septocaine — contains the same concentration of articaine with a higher concentration of epinephrine (1:100,000) compared to Septocaine —. This may be significant if the goal is to limit exposure to cardiovascular stresses from the higher doses of epinephrine contained in Septocaine —

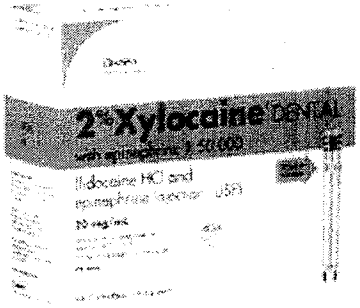
Additionally, it was noted by the Expert Panel that a numeric modifier can cause confusion for practitioners because there are no units associated with the number (e.g., mg, mL, etc.). Thus, a practitioner may think that the number represents the number of doses, the strength, or volume. Upon consideration, DMETS believes that the use of a numeric modifier without reference to a unit of measure may be used safely in this context given the characteristics of this drug product. As noted above, the modifier " —)" does not accurately reflect the combination product and should be revised. An Expert Panel member questioned how the sponsor would name the drug product if the Articaine per-cent was changed. For example, if the sponsor plans to market a 5% product with epinephrine 1:100,000, what would they name it? Septocaine 5/100? Thus, the numeric modifier can also create difficulty in naming future products.

DMETS recommends the sponsor use a similar naming convention used for the dental product Xylocaine with epinephrine. The product is named 2% Xylocaine with epinephrine 1:50,000 and 2% Xylocaine with epinephrine 1:100,000. Additionally, the labels and labeling of the product are in accordance with the ADA anesthesia color codes. The product name for 2% Xylocaine with epinephrine 1:50,000 appears on a green background and the 2% Xylocaine with epinephrine 1:100,000 appears on a red background. DMETS believes that the naming convention used for the drug product is the most accurate representation of the medication and we have not had any reported cases of name confusion with this naming convention.

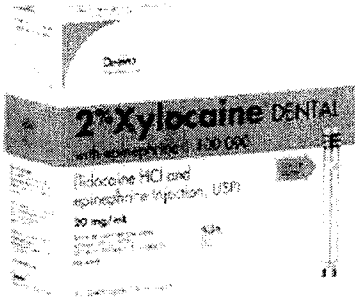
Additionally, DMETS reviewed the container labels, carton and insert labeling of Septocaine from a safety perspective and we identified the following areas of possible improvement, which may minimize potential user error.

A. GENERAL COMMENT

DMETS objects to the proprietary name Septocaine — because it is a combination product and the modifier does not clearly indicate which ingredient it is modifying (articaine or epinephrine). Furthermore, it does not accurately define the concentration of the product in which it describes (epinephrine). We do not recommend not using " — as a modifier. We recommend keeping the Septocaine name and adding "with epinephrine 1:100,000 [or 1;200,000]". The products can be differentiated by highlighting the different epinephrine concentrations for each Septocaine product in accordance with the ADA anesthesia color codes. This is similar to the naming convention for 2% Xylocaine with epinephrine 1:50,000 and 2% Xylocaine with epinephrine 1:100,000 which are local anesthetic combination injections for dental use. Both Xylocaine products contain lidocaine HCl 2%, yet the epinephrine concentrations vary (epinephrine 1:50,000 and epinephrine 1:100,000) (see examples below). This is similar to Septocaine and Septocaine — because the active ingredient is constant (articaine 4%) and the epinephrine concentration is variable (1:100,000 and 1:200,000).



with epinephrine 1:50,000



with epinephrine 1:100,000

B. CONTAINER LABEL

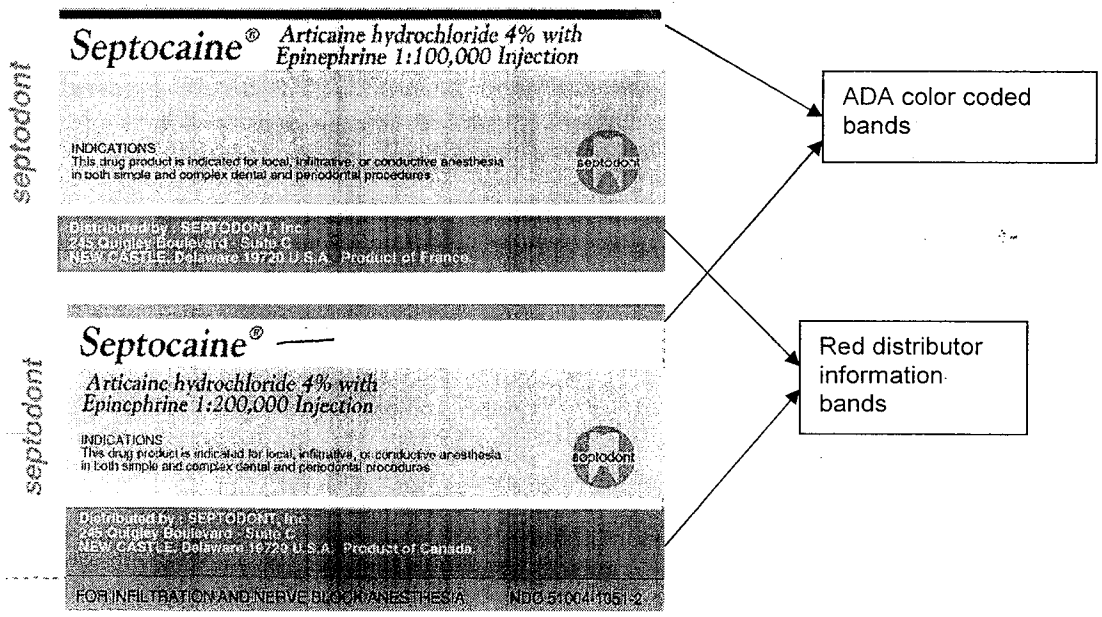
1. Increase the prominence of the established name to at least ½ the size of the proprietary name per 21 CFR 201.10(g)(2).

2. Ensure that the Pantone 877C color is approved by the ADA standards board for color coding. It is important to differentiate the epinephrine concentration of Septocaine — from the currently marketed Septocaine. The sponsor should consult with the American Dental Association in order to ensure that an appropriate anesthesia color code is used to differentiate the epinephrine concentrations.

Appears This Way
On Original

C. CARTON LABELING

1. We note that the carton labels for Septocaine and Septocaine — will be differentiated only by the different color codes bands on the product. The products appear almost identical. In order to minimize selection errors, we recommend differentiating the appearance of the cartons (e.g., remove the red band that contains the distributor information on the new drug product).



2. The net quantity statement reads as follows: "50 cartridges, ——— 1.7 mL." The phrase, ' ——— ', is irrelevant and may be confusing. According to the "How Supplied" section of the package insert, Septocaine — will be available in 1.7 mL glass cartridges. Remove the phrase ' ——— ' and revise the net quantity to read as: "50 cartridges: 1.7 mL each".

D. INSERT LABELING

No comment.

Appears This Way
On Original

Appendix A – Septocaine — Prescription Study Results

Written Outpatient	Written Inpatient	Verbal
Septocaine	Septacaine	Ceptacaine
Septocaine	Septacaine	Cepticaine
Septocaine	Septacaine	Ceptikane
Septocaine	Septacaine	Septacaine
Septocaine	Septacaine	Septacaine
Septocaine	septacaine	septacaine
Septocaine	Septacaine	Septacaine
Septocaine	Septacaine	Septacaine
septocaine	Septacaine	Septicaine
septocaine	Septacaine	septicaine
Septocaine	Septacaine	Septicaine
Septocaine	septacaine	Septicaine
Septocaine	Septocaine	Septicaine
Septocaine	Septocaine	Septocaine
Septocaine	Septocaine	Septocaine
Septocaine	Septocaine	Septocaine
Septocaine	septocaine	Septocaine
Septocaine	Septocaine	Septracaine
Styptocaine		Subdicaine
		Suptacaine