

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-466

PROPRIETARY NAME REVIEW(S)



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: October 9, 2009

To: Bob Rappaport, MD, Director
Division of Anesthesia, Analgesia and Rheumatology
Products

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(DMEPA)

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(DMEPA)

Subject: Proprietary Name Review

Drug Name(s): (b) (4)
Articaine Hydrochloride 4% with Epinephrine Bitartrate
1:100,000 Injection and
Articaine Hydrochloride 4% with Epinephrine Bitartrate
1:200,000 Injection
1.8 mL cartridges

Application Type/Number: NDA # 22-466

Applicant: Pierrell S.p.A.

OSE RCM #: 2009-1237

This document contains proprietary and confidential information that should not be released to the public.

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EXECUTIVE SUMMARY

Capacaine is the proposed name for Articaine Hydrochloride with Epinephrine Bitartrate Injection. The proposed name was evaluated from a safety and promotional perspective based on the product characteristics provided by the Applicant. We sought input from pertinent disciplines involved with the review of this application and considered it accordingly. As a result of the Division of Medication Error Prevention and Analysis (DMEPA) evaluation, we find the proposed name Capacaine vulnerable to name confusion with the existing product Carbocaine.

Additionally, our evaluation of the proposed proprietary name, Capacaine, noted the use of the United States Adopted Name (USAN) stem '-caine.' The USAN stem '-caine' is reserved for use in the established names of local anesthetic products, and its presence in the proposed proprietary name is inappropriate. Additionally, the use of stems in proprietary names can result in multiple similar proprietary names and proprietary names that are similar to established names, thus increasing the risk of confusion among those drugs. This confusion may compromise patient safety. Therefore, USAN stems should not be incorporated into proprietary names. Thus, the Division of Medication Error Prevention and Analysis (DMEPA) objects to the use of the proposed proprietary name, Capacaine.

1 BACKGROUND

1.1 INTRODUCTION

This consult was written in response to the submission dated July 14, 2009, requesting a review of the proposed proprietary name, Capacaine. The proposed name, Capacaine, is evaluated for potential name confusion with other proprietary or established drug names. The proposed draft labels and labeling for Capacaine were evaluated in a separate review, OSE Review # 2008-2060, dated August 24, 2009.

1.2 REGULATORY HISTORY

The original New Drug Application (NDA) application for this drug product was submitted by the Applicant on November 25, 2008. Septocaine (NDA # 20-971 and 22-010) is the reference listed drug product that has been referenced under 505(b)(2) for this proposed product.

1.3 PRODUCT INFORMATION

Capacaine (Articaine Hydrochloride 4% with Epinephrine Bitartrate 1:100,000 Injection and Articaine Hydrochloride 4% with Epinephrine Bitartrate 1:200,000 Injection) is a local dental anesthetic of the amide type indicated for local, infiltrative, or conductive anesthesia in both simple and complex dental procedures. The epinephrine is added as a vasoconstrictor to slow absorption into the general circulation and thus prolong maintenance of an active tissue concentration of articaine. Capacaine is a sterile injection containing 40 milligrams/mL articaine hydrochloride and 10 micrograms/mL (1:100,000 product) or 5 micrograms/mL (1:200,000 product) of epinephrine bitartrate as the free base.

The recommended doses of Capacaine via submucosal infiltration and/or nerve block are administered via dental cartridges. The doses are based on the articaine HCl component and are proposed as follows in the insert labeling:

- Normal healthy adults:
 - Infiltration: 0.5 mL-2.5 mL (20 mg-100 mg articaine HCl)
 - Nerve block: 0.5 mL-3.4 mL (20 mg-136 mg articaine HCl)
 - Oral surgery: 1 mL-5.1 mL (40 mg-204 mg articaine HCl)

Other volumes within the maximum recommended dose may be used.

- Maximum recommended dosages:
 - Children 4-16 years and adults: 7 mg/kg (0.175 mL/kg)

Capacaine (articaine HCl 4% with epinephrine 1:100,000 or 1:200,000 injection) is available in 1.8 mL glass cartridges, in boxes of 100 cartridges. They will be stocked primarily in dental offices and clinics for use in those settings. Capacaine cartridges should be stored below 25°C (77°F).

2 METHODS AND MATERIALS

This section describes the methods and materials used by DMEPA staff to conduct a proprietary name risk assessment. The primary focus for this assessment is to identify and remedy potential sources of medication error prior to drug approval. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.¹

2.1 PROPRIETARY NAME RISK ASSESSMENT

FDA's Proprietary Name Risk Assessment considers the potential for confusion between the proposed proprietary name, Capacaine, and the proprietary and established names of drug products existing in the marketplace and those pending IND, NDA, BLA and ANDA products currently under review by CDER.

For the proprietary name, Capacaine, the DMEPA staff search a standard set of databases and information sources to identify names with orthographic and phonetic similarity (see Section 2.1.1.1) and held an CDER Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name (see Section 2.1.1.2).

The Safety Evaluator assigned to the Proprietary Name Risk Assessment is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name (see Section 2.1.3). The overall risk assessment is based on the findings of a Failure Mode and Effects Analysis (FMEA) of the proprietary name, and is focused on the avoidance of medication errors. FMEA is a systematic tool for evaluating a process and identifying where and how it might fail.² FMEA is used to analyze whether the drug names identified with look- or sound-alike similarity to the proposed name could cause confusion that subsequently leads to medication errors in the clinical setting. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient

¹ National Coordinating Council for Medication Error Reporting and Prevention. <http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

² Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

harm while the medication is in the control of the health care professional, patient, or consumer.³ DMEPA uses the clinical expertise of its staff to anticipate the conditions of the clinical setting that the product is likely to be used in based on the characteristics of the proposed product.

In addition, the product characteristics provide the context for the verbal and written communication of the drug names and can interact with the orthographic and phonetic attributes of the names to increase the risk of confusion when there is overlap, or, in some instances, decrease the risk of confusion by helping to differentiate the products through dissimilarity. As such, the staff considers the product characteristics associated with the proposed drug throughout the risk assessment, since the product characteristics of the proposed may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed drug name include, but are not limited to established name of the proposed product, the proposed indication, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. Because drug name confusion can occur at any point in the medication use process, DMEPA considers the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.⁴

2.1.1 Search Criteria

The DMEPA staff considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted as outlined in Appendix A.

For this review, particular consideration was given to drug names beginning with the letter ‘C’ when searching to identify potentially similar drug names, as 75% of the confused drug names reported by the United States Pharmacopeia-Institute of Medication Practices (USP-ISMP) Medication Error Reporting Program involve pairs beginning with the same letter.^{5,6}

To identify drug names that may look similar to Capacaine, the DMEPA staff also consider the orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (9 letters), upstrokes (one, capital letter ‘C’), down strokes (one, letter ‘p’), cross-strokes (none), and dotted letters (one, letter ‘i’). Additionally, several letters in Capacaine may be vulnerable to ambiguity when scripted (see Appendix B). As such, the staff also considers these alternate appearances when identifying drug names that may look similar to Capacaine.

³ National Coordinating Council for Medication Error Reporting and Prevention. <http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

⁴ Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

⁵ Institute for Safe Medication Practices. Confused Drug name List (1996-2006). Available at <http://www.ismp.org/Tools/confuseddrugnames.pdf>

⁶ Kondrack, G and Dorr, B. Automatic Identification of Confusable Drug Names. Artificial Intelligence in Medicine (2005)

When searching to identify potential names that may sound similar to Capacaine, the DMEPA staff searches for names with similar number of syllables (three), stresses (CAP-a-caine, cap-A-caine, cap-a-CAINE), and placement of vowel and consonant sounds. DMEPA also considers the Applicant's intended pronunciation of the name when it is provided. Additionally, the DMEPA staff considers that pronunciation of parts of the name can vary (See Appendix B). Furthermore, names are often mispronounced and/or spoken with regional accents and dialects, so other potential pronunciations of the name are considered.

The DMEPA staff also consider the product characteristics associated with the proposed drug throughout the identification of similar drug names, since the product characteristics of the proposed drug ultimately determine the use of the product in the clinical practice setting. For this review, the DMEPA staff were provided with the following information about the proposed product: the proposed proprietary name (Capacaine), the established name (Articaine HCl with Epinephrine bitartrate), proposed indication (local anesthesia), strength (4%/1:100,000 or 4%/1:200,000), dose (individualized), frequency of administration (intra-procedural), route of administration (submucosal infiltration and/or nerve block) and dosage form of the product (injection). Appendix A provides a more detailed listing of the product characteristics the medication error staff generally takes into consideration.

Lastly, the DMEPA staff also considers the potential for the proposed name to inadvertently function as a source of error for reasons other than name confusion. Post-marketing experience has demonstrated that proprietary names (or components of the proprietary name) can be a source of error in a variety of ways. As such, these broader safety implications of the name are considered and evaluated throughout this assessment and the medication error staff provides additional comments related to the safety of the proposed name or product based on their professional experience with medication errors.

2.1.1.1 Database and Information Sources

The proposed proprietary name, Capacaine, was provided to the DMEPA staff to conduct a search of the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to Capacaine using the criteria outlined in Section 2.1.1. A standard description of the databases used in the searches is provided in Section 7. To complement the process, the DMEPA staff uses a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, DMEPA staff reviews the United States Adopted Names (USAN) stem list to determine if any USAN stems are present within the proprietary name. The findings of the individual Safety Evaluators were then pooled and presented to the Expert Panel.

2.1.1.2 CDER Expert Panel Discussion

An Expert Panel Discussion is held by DMEPA to gather CDER professional opinions on the safety of the product and the proprietary name, Capacaine. Potential concerns regarding drug marketing and promotion related to the proposed names are also discussed. This group is composed of DMEPA staff and representatives from the Division of Drug Marketing, Advertising, and Communications (DDMAC).

The pooled results of DMEPA staff were presented to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend the addition of names, additional searches by the Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

2.1.2 Comments from the Division of Anesthesia, Analgesia, and Rheumatology Products

DMEPA requests the regulatory division in the Office of New Drugs responsible for the application for their comments and/or clinical/other concerns on the proposed proprietary name at the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with DDMAC's decision on the name. Any comments or concerns are addressed in the safety evaluator's assessment.

The Review Division is contacted a second time following our analysis of the proposed name. At this point, DMEPA conveys their decision to accept or reject the name. The regulatory division is requested to concur /not concur with DMEPA's final decision.

2.1.3 Safety Evaluator Risk Assessment of the Proposed Proprietary Name

Based on the criteria set forth in Section 2.1.1, the Safety Evaluator Risk Assessment applies their individual expertise gained from evaluating medication errors reported to FDA to conduct a Failure Mode and Effects Analysis and provide an overall risk of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.⁷ When applying FMEA to assess the risk of a proposed proprietary name, the Division of Medication Error Prevention and Analysis seeks to evaluate the potential for a proposed name to be confused with another drug name as a result of the name confusion and cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to look- or sound-alike drug names prior to approval, where actions to overcome these issues are easier and more effective than remedies available in the post-approval phase.

In order to perform an FMEA of the proposed name, the Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is not yet marketed, the Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product characteristics listed in Appendix A. The Safety Evaluator then analyzes the proposed proprietary name in the context of the usual practice setting and works to identify potential failure modes and the effects associated with the failure modes.

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, expert panel evaluation, and studies, and identifies potential failure modes by asking:

“Is the name Capacaine convincing similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting?”

An affirmative answer indicates a failure mode and represents a potential for Capacaine to be confused with another proprietary or established drug name because of look- or sound-alike

⁷ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

similarity. If the answer to the question is no, the Safety Evaluator is not convinced that the names possesses similarity that would cause confusion at any point in the medication use system and the name is eliminated from further review.

In the second stage of the Risk Assessment, all potential failure modes are evaluated to determine the likely *effect* of the drug name confusion, by asking:

“Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?”

The answer to this question is a central component of the Safety Evaluator’s overall risk assessment of the proprietary name. If the Safety Evaluator determines through FMEA that the name similarity would ultimately not be a source of medication errors in the usual practice setting, the name is eliminated from further analysis. However, if the Safety Evaluator determines through FMEA that the name similarity could ultimately cause medication errors in the usual practice setting, the Safety Evaluator will then recommend that an alternate proprietary name be used. In rare instances, the FMEA findings may provide other risk-reduction strategies, such as product reformulation to avoid an overlap in strength or an alternate modifier designation may be recommended as a means of reducing the risk of medication errors resulting from drug name confusion.

DMEPA will object to the use of proposed proprietary name when the one or more of the following conditions are identified in the Safety Evaluator’s Risk Assessment:

1. DDMAC finds the proposed proprietary name misleading from a promotional perspective, and the review Division concurs with DDMAC’s findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a trade name or otherwise. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n)].
2. The Division of Medication Error Prevention and Analysis identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].
3. FMEA identifies potential for confusion between the proposed proprietary name and other proprietary or established drug names, and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.
4. The proposed proprietary name contains a USAN stem, particularly in a manner that is contradictory to the USAN Council’s definition.
5. DMEPA identifies a potential source of medication error within the proposed proprietary name. The proprietary name may be misleading, or inadvertently introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product.

In the event that DMEPA objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, DMEPA will provide a contingency objection based on the date of approval: whichever product is

awarded approval first has the right to use the name, while DMEPA will recommend that the second product to reach approval seek an alternative name.

If none of these conditions are met, then DMEPA will not object to the use of the proprietary name. If any of these conditions are met, then DMEPA will object to the use of the proprietary name. The threshold set for objection to the proposed proprietary name may seem low to the Applicant; however, the safety concerns set forth in criteria 1 through 5 are supported either by FDA Regulation or by external healthcare authorities, including the Institute of Medicine (IOM), World Health Organization (WHO), Joint Commission for Healthcare Organizations (JCAHO), and Institute for Safe Medication Practices (ISMP), who have examined medication errors resulting from look- or sound-alike drug names and called for Regulatory Authorities to address the issue prior to approval.

Furthermore, DMEPA contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and preventable source of medication error that, in many instances, can be identified and remedied prior to approval to avoid patient harm.

Additionally, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to remedy post-approval. Educational efforts and so on are low-leverage strategies that have proven to have limited effectiveness at alleviating the medication errors involving drug name confusion. Higher-leverage strategies, such as drug name changes, have been undertaken in the past; but at great financial cost to the Applicant, and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for the approving the error-prone proprietary name. Moreover, even after Applicants have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioner's vocabulary, and as such, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, DMEPA believes that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval (see limitations of the process).

If DMEPA objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the FMEA process is used to identify strategies to reduce the risk of medication errors. DMEPA is likely to recommend that the Applicant select an alternative proprietary name and submit the alternate name to the Agency for DMEPA to review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name, and so DMEPA may be able to provide the Sponsor with recommendations that reduce or eliminate the potential for error would render the proposed name acceptable.

3 RESULTS

3.1 PROPRIETARY NAME RISK ASSESSMENT

3.1.1 Database and Information Sources

Our search identified a total of seventeen names as having some similarity to the name Capacaine.

Fifteen names were thought to look like Capacaine, which include: Bupivacaine, Paracaine, Americaine, Alphacaine, Lopressor, Lidocaine, Cepazine, Cepacaina, Cepacaine, Capsaicin, Capsicum, Cuprimine, Copaxone, Carbocaine, and Septocaine.

One name was thought to sound like Capacaine (Capoten). One name was thought to look and sound like Capacaine (Cetacaine).

The Division of Medication Error Prevention and Analysis identified the USAN stem ‘-caine’ in the name Capacaine as of August 29, 2009. The stem ‘-caine’ is intended for use in the established names of local anesthetic products.

3.1.2 CDER Expert Panel Discussion

The Expert Panel reviewed the pool of names identified by DMEPA staff (see section 3.1 above), and noted no additional names thought to have orthographic or phonetic similarity to Capacaine and have the potential for confusion.

DDMAC had no concerns regarding the proposed name from a promotional perspective, and did not offer any additional comments relating to the proposed name.

3.1.3 Comments from the Division of Anesthesia, Analgesia, and Rheumatology Products

In response to the OSE July 15, 2009 e-mail, DAARP did not forward any comments and/or clinical/other concerns on the proposed name at the initial phase of the name review.

DMEPA notified DAARP via e-mail that we objected to the proposed proprietary name, Capacaine, on September 10, 2009. Per e-mail correspondence from the DAARP on September 16, 2009, they indicated they concur with our assessment of the proposed name, Capacaine.

3.1.4 Safety Evaluator Risk Assessment

Independent searches by the primary Safety Evaluator identified three additional names: Caproamin, Caprin, and Cyclaine, which were thought to look similar to Capacaine and represent a potential source of drug name confusion. As such, a total of twenty names were analyzed to determine if the drug names could be confused with Capacaine, and if the drug name confusion would likely result in a medication error.

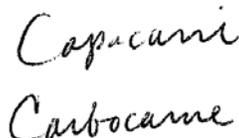
Twelve names were not analyzed further for the following reasons:

- Seven names do not have convincing orthographic and/or phonetic similarity and should not result in medication errors with Capacaine (see Appendix C).
- Five names are marketed in foreign countries (see Appendix D)

The remaining eight names were determined to have some orthographic and/or phonetic similarity to Capacaine, and thus determined to present some risk for confusion. Failure Mode and Effect Analysis (FMEA) was then applied to determine if the proposed name, Capacaine, could potentially be confused with any of the eight names and lead to medication error. This analysis determined that the name similarity between Capacaine and the identified names was unlikely to result in a medication error with the seven of the eight products identified for the reasons presented in Appendices E through G. However, this analysis determined that Capacaine is vulnerable to confusion with the remaining product, Carbocaine (see Section 4).

4 DISCUSSION

DDMAC did not identify any issues with the proposed name, Capacaine, from a promotional perspective, and the Review Division did not have any other issues with the proposed name. DMEPA identified and evaluated twenty names for their potential similarity to the proposed name, Capacaine. Our FMEA indicates that the proposed name, Capacaine is not likely to result in name confusion that could lead to medication errors with nineteen of the identified products. However, this analysis determined that Capacaine is vulnerable to name confusion with the remaining product, Carbocaine.



The image shows two lines of handwritten text in cursive script. The top line reads 'Capacaine' and the bottom line reads 'Carbocaine'. The two words are written in a similar style, highlighting their visual similarity.

Carbocaine and Capacaine can look and sound similar. However, it is not likely that prescriptions will be written for either product. Both Carbocaine and Capacaine may be administered to the same population for the same indication (local dental anesthesia), thus the greatest potential for confusion and medication error exists at the point of use in dental offices and dental surgical suites. Offices may stock both products in the same location increasing the potential for a selection error. Dental personnel will select the drug cartridges for use prior to the procedure. Medication errors may occur if the wrong cartridge is selected due to name similarity. Furthermore, both Carbocaine and Capacaine have the same cartridge size (1.8 mL) and therefore will look similar, so it will be difficult to determine if a selection error has occurred, particularly if the cartridge has already been loaded into an injector.

Although both products have different strengths and dosing recommendations, the strengths and/or doses are not usually written down prior to use where they can be helpful to differentiate between the two products beforehand. The dentist or staff may write the doses administered throughout the procedure down during the procedure. Additionally, although both products' labeling contains recommendations to calculate a dose, based upon the procedure, intensity of anesthesia needed, duration of anesthesia, and the patient; often the typical practice is to round the dose to the number of 1.8 mL cartridges to administer. Thus, dental staff may only be directed to procure and prepare X cartridges of Carbocaine/Capacaine for the dental procedure.

Given the similarity of this name pair and the overwhelming similarity of the product characteristics, our analysis indicates that medication errors are likely to occur with these products if the name Capacaine is approved.

Additionally, the proposed proprietary name, Capacaine, contains the United States Adopted Name (USAN) stem, '-caine'. This stem is used by USAN Council to indicate local anesthetic products. Although the proposed product, Capacaine, is a local anesthetic product which is consistent with the intended USAN meaning, the USAN Council uses this stem for established names only. The use of stems in proprietary names can result in multiple similar proprietary names and proprietary names that are similar to established names, thus increasing the chance of confusion among those drugs which may compromise patient safety. Thus, this practice is unacceptable and the Division of Medication Error Prevention and Analysis (DMEPA) also objects to the use of the proposed proprietary name, Capacaine, because it contains the USAN stems '-caine'.

The USAN Council (tri-sponsored by the American Medical Association (AMA), the United States Pharmacopeial Convention (USP), and the American Pharmacists Association (APhA)) works closely with the International Nonproprietary Name (INN) Programme of the World Health Organization (WHO) and various national nomenclature groups to achieve global standardization and unification of drug nomenclature and related rules with the goal of ensuring that drug information is communicated accurately and unambiguously.

The goal of the USAN program is to provide meaningful, informative designations for compounds, enhancing correct prescribing practices and patient safety. The listing of USAN stems represents common stems for which chemical and/or pharmacologic parameters have been established. These stems and their definitions, approved by the USAN Council, are recommended for use in coining new nonproprietary names for drugs that belong to an established series of related agents. By adopting this system, similar compounds maintain a common "family" name that provides immediate recognition.

Because the USAN stems are intended to indicate a pharmacological or chemical trait of a drug, a single stem will be applicable to multiple drug products. Use of these stems in proprietary names, even when used consistently with the USAN meaning, can result in multiple similar proprietary names and proprietary names that are similar to established names, thus increasing the chance of confusion among those drugs. To reduce the potential for confusion, USAN stems should not be incorporated into proprietary names. FDA recommends that applicants screen potential proprietary names against the USAN stem list and eliminate those that would incorporate USAN stems.

5 CONCLUSIONS AND RECOMMENDATIONS

The Division of Medication Error Prevention and Analysis (DMEPA) objects to the use of the proposed proprietary name, Capacaine, because it contains the USAN stem '-caine' and because it is vulnerable to name confusion with the currently marketed product, Carbocaine'. Accordingly, the proposed name Capacaine is unacceptable for this product.

If you have further questions or need clarifications, please contact Abolade Adeolu, OSE Project Manager, at 301-796-4264.

5.1 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Capacaine, and have concluded that this name is unacceptable for the following reasons.

The proposed proprietary name, Capacaine contains the United States Adopted Name (USAN) stem '-caine'. This stem is used by USAN to indicate a local anesthetic product. Although Capacaine is a local anesthetic drug product and its use is consistent with the intended USAN meaning, the USAN Council uses this stem for established names only.

The use of stems in proprietary names can result in multiple similar proprietary names and proprietary names that are similar to established names, thus increasing the risk of confusion among those drugs. This confusion may compromise patient safety. To reduce the potential for confusion, USAN stems should not be incorporated into proprietary names. We recommend you

screen potential proprietary names against the USAN stem list and eliminate those that incorporate USAN stems.

Additionally, the proposed proprietary name Capacaine was found to be orthographically and phonetically similar to the proprietary name, Carbocaine. The orthographic similarities of this name pair stem from the similar length of the name (9 letters vs. 10 letters), identical beginning ‘Ca’ and ending ‘caine’ letters. Although the lower case ‘b’ and the lower case ‘p’ usually represent an upstroke in Carbocaine and down stroke in Capacaine respectively, if either expression is blunted, these orthographic differences may not be sufficient to differentiate the two proprietary names.

Phonetically, there are minimal differences between the two proprietary names especially since they share identical beginning and ending sounds. Additionally, the infixes ‘bo’ vs. ‘pa’ can be phonetically similar. In addition to the orthographic and phonetic similarity the products share similar product characteristics such as similar indication of use and same setting of use. The appearance of the product is similar as well. Thus the greatest potential for confusion and medication error exists at the point of use in dental offices and surgical suites. Offices may stock both products in the same location, increasing the potential for a selection error. Dental personnel will select the drug cartridges for use prior to the procedure. Medication errors may occur if the wrong cartridge is selected due to name similarity. Furthermore, both Carbocaine and Capacaine are available in the same cartridge size (1.8 mL) and may look similar once a cartridge has been loaded into an injector.

Although the products have different strengths and dosing recommendations, the strengths and/or doses may not be written in the chart or on an order prior to use when they can be used to differentiate the two products. Thus, dental staff may only be directed to procure and prepare ‘X’ number of Carbocaine/Capacaine cartridges for the dental procedure. Given the similarity of this name pair and the similarity of the product characteristics, our analysis indicates that medication errors are likely to occur with these products if the name Capacaine is approved.

6 REFERENCES

1. *Micromedex Integrated Index* (<http://weblern/>)

Contains a variety of databases covering pharmacology, therapeutics, toxicology and diagnostics.

2. *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. Likewise, an orthographic algorithm exists which operates in a similar fashion. This is a database which was created for DMETS, FDA.

3. *Drug Facts and Comparisons, online version, St. Louis, MO* (<http://weblern/>)

Drug Facts and Comparisons is a compendium organized by therapeutic Course; contains monographs on prescription and OTC drugs, with charts comparing similar products.

4. *AMF Decision Support System [DSS]*

DSS is a government database used to track individual submissions and assignments in review divisions.

5. Division of Medication Error Prevention and Analysis proprietary name consultation requests

This is a list of proposed and pending names that is generated by DMEPA from the Access database/tracking system.

6. Drugs@FDA (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>)

Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved [brand name](#) and [generic drugs](#) and [therapeutic biological products](#); [prescription](#) and [over-the-counter](#) human drugs and [therapeutic biologicals](#), [discontinued drugs](#) and “Chemical Blue 6” approvals.

7. Electronic online version of the FDA Orange Book (<http://www.fda.gov/cder/ob/default.htm>)

Provides a compilation of approved drug products with therapeutic equivalence evaluations.

8. U. S. Patent and Trademark Office website <http://www.uspto.gov>.

Provides information regarding patent and trademarks.

9. Clinical Pharmacology Online (<http://weblern/>)

Contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. Provides a keyword search engine.

10. Data provided by Thomson & Thomson’s SAEGIS™ Online Service, available at www.thomson-thomson.com

The Pharma In-Use Search database contains over 400,000 unique pharmaceutical trademarks and tradenames that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

11. Natural Medicines Comprehensive Databases (<http://weblern/>)

Contains up-to-date clinical data on the natural medicines, herbal medicines, and dietary supplements used in the western world.

12. Stat!Ref (<http://weblern/>)

Contains full-text information from approximately 30 texts. Includes tables and references. Among the database titles are: Handbook of Adverse Drug Interactions, Rudolphs Pediatrics, Basic Clinical Pharmacology and Dictionary of Medical Acronyms Abbreviations.

13. USAN Stems (<http://www.ama-assn.org/ama/pub/category/4782.html>)

List contains all the recognized USAN stems.

14. Red Book Pharmacy’s Fundamental Reference

Contains prices and product information for prescription, over-the-counter drugs, medical devices, and accessories.

15. Lexi-Comp (www.pharmacist.com)

A web-based searchable version of the Drug Information Handbook.

16. Medical Abbreviations Book

Contains commonly used medical abbreviations and their definitions.

APPENDICES

Appendix A:

The medication error staff considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. DMEPA also compare the spelling of the proposed proprietary name with the proprietary and established name of existing and proposed drug products because similarly spelled names may have greater likelihood to sound similar to one another when spoken or look similar to one another when scripted. The medication error staff also examines the orthographic appearance of the proposed name using a number of different handwriting samples. Handwritten communication of drug names has a long-standing association with drug name confusion. Handwriting can cause similarly *and* dissimilarly spelled drug name pairs to appear very similar to one another and the similar appearance of drug names when scripted has lead to medication errors. The medication error staff apply their expertise gained from root-cause analysis of such medication errors to identify sources of ambiguity within the name that could be introduced when scripting (i.e. “T” may look like “F,” lower case ‘a’ looks like a lower case ‘u,’ etc), along with other orthographic attributes that determine the overall appearance of the drug name when scripted (see detail in Table 1 below). Additionally, since verbal communication of medication names is common in clinical settings, the medication error staff compares the pronunciation of the proposed proprietary name with the pronunciation of other drug names. If provided, DMEPA will consider the Sponsor’s intended pronunciation of the proprietary name. However, because the Sponsor has little control over how the name will be spoken in practice, DMEPA also considers a variety of pronunciations that could occur in the English language.

Table 1. Criteria used to identify drug names that look- or sound-similar to a proposed proprietary name

Type of similarity	Considerations when searching the databases		
	Potential causes of drug name similarity	Attributes examined to identify similar drug names	Potential Effects
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	<ul style="list-style-type: none"> Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication Names may look similar when scripted and lead to drug name confusion in written communication
	Orthographic similarity	Similar spelling Length of the name Upstrokes Downstrokes	<ul style="list-style-type: none"> Names may look similar when scripted, and lead to drug name confusion in written communication

		<p>Cross-strokes</p> <p>Dotted letters</p> <p>Ambiguity introduced by scripting letters</p> <p>Overlapping product characteristics</p>	
Sound-alike	Phonetic similarity	<p>Identical prefix</p> <p>Identical infix</p> <p>Identical suffix</p> <p>Number of syllables</p> <p>Stresses</p> <p>Placement of vowel sounds</p> <p>Placement of consonant sounds</p> <p>Overlapping product characteristics</p>	<ul style="list-style-type: none"> Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Appendix B: Letters with possible orthographic or phonetic misinterpretation

Letters in Root Name, Capacaine	Scripted may appear as	Spoken may be interpreted as
Capital 'C'	'A', 'O'	'K', 'S'
First letter lower case 'c'	'e', 'i', 'r'	
lower case 'e'	'a', 'u', 'i', 'o'	any vowel
lower case 'p'	'j', 'y', 'f'	any vowel
lower case 'c'	'i', 'r'	'k', 's'
lower case 'i'	'a', 'e', 'u', 'o'	Any vowel
lower case 'a'	'e', 'o' or 'u'	Any vowel
lower case 'n'	'm', 'u', 'r'	'm', 'u'

Appendix C: Names Lacking Orthographic and/or Phonetic Similarity with Capacaine.

Name	Name
Capoten	Alphacaine
Bupivacaine	Lopressor
Paracaine	Lidocaine
Americaine	

Appendix D: Proprietary or Established Names used only in Foreign Countries

Proprietary Name	Similarity to Capacaine	Country	Description
Cépazine	Orthographic	France	Cefurozime axetil
Cepacaina	Orthographic	Mexico, Brazil	Benzocaine, Cetyl Pyridinium Chloride
Cepacaine	Orthographic	Australia, New Zealand, South Africa	Benzocaine, Cetyl Pyridinium Chloride
Caprin	Orthographic	India, Australia	Heparin
Caproamin	Orthographic	Spain, Venezuela	Aminocaproic acid

Appendix E: Discontinued Products with no generic equivalent

Proprietary Name	Similarity to Capacaine	Description
Cyclaine	orthographic	Hexylcaine HCl

Appendix F: Products with no numerical overlap in strength or dose

Product name with potential for confusion	Similarity to Capacaine	Strength	Usual Dose
Capacaine (Articaine with Epinephrine) Injection	N/A	Articaine Hydrochloride 4% with Epinephrine Bitartrate 1:100,000, 1.8 mL cartridges Articaine Hydrochloride 4% with Epinephrine Bitartrate 1:200,000, 1.8 mL cartridges	Doses up to 7 mg/kg (0.175 mL/kg), based on articaine component, are used for local anesthesia (submucosal infiltration and/or nerve block) during a dental procedure.
Capsaicin	Orthographic	Cream, topical: 0.025% (60 g); 0.075% (60 g) Capzasin-P®: 0.025% (45 g) Capzasin-HP®: 0.075% (45 g) Zostrix®: 0.025% (60 g) Zostrix®-HP: 0.075% (60 g) Zostrix® Neuropathy: 0.25% (60 g) [in Lidocare™ vehicle] Lotion, topical: DiabetAid Pain and Tingling Relief: 0.025% (120 mL)	Apply to affected area at least 3-4 times per day
Capsicum frutescens (Cayenne: herbal preparation for arthritis pain, capsaicin is a derivative)	Orthographic	Various topical preparations. Prescription version is capsaicin	Apply to affected area three to four times daily
Cuprimine (Penicillamine)	Orthographic	Capsules: 250 mg	Rheumatoid arthritis: Oral: 250 mg/day, may increase dose at 1- to 3-month intervals up to 1-1.5 g/day Wilson's disease: Oral: 250 mg 4 times/day. Titrated to maintain urinary copper excretion >2 mg/day;

Product name with potential for confusion	Similarity to Capacaine	Strength	Usual Dose
Capacaine (Articaine with Epinephrine) Injection	N/A	Articaine Hydrochloride 4% with Epinephrine Bitartrate 1:100,000, 1.8 mL cartridges Articaine Hydrochloride 4% with Epinephrine Bitartrate 1:200,000, 1.8 mL cartridges	Doses up to 7 mg/kg (0.175 mL/kg), based on articaine component, are used for local anesthesia (submucosal infiltration and/or nerve block) during a dental procedure.
Cetacaine (Benzocaine, Butamben, Tetracaine HCl)	Orthographic and Phonetic	Aerosol, topical [spray]: Cetacaine®: benzocaine 14%, butamben 2%, and tetracaine hydrochloride 2% (56 g) Gel, topical: Cetacaine®: benzocaine 14%, butamben 2%, and tetracaine hydrochloride 2% (29 g) Liquid, topical: Cetacaine®: benzocaine 14%, butamben 2%, and tetracaine hydrochloride 2% (56 g)	Aerosol: Apply for ≤1 second; use of sprays >2 seconds is contraindicated Gel: Apply ~1/2 inch (13 mm) x 3/16 inch (5 mm); application of >1 inch (26 cm) x 3/16 inch (5 mm) is contraindicated Liquid: Apply 6-7 drops (0.2 mL); application of >12-14 drops (0.4 mL) is contraindicated
Copaxone (Glatiramer Acetate)	Orthographic	Injection, solution: 20 mg/mL (1 mL) [prefilled syringe; contains mannitol; packaged with alcohol pads]	20 mg daily via subcutaneous injection

Appendix G: Name with numerical similarity in strength or dose.

<p>Capacaine (Articaine with Epinephrine) Injection</p>	<p>Articaine Hydrochloride 4% with Epinephrine Bitartrate 1:100,000 1.8 mL cartridges</p> <p>Articaine Hydrochloride 4% with Epinephrine Bitartrate 1:200,000 1.8 mL cartridges</p>	<p>Doses up to 7 mg/kg (0.175 mL/kg), based on articaine component, are used for local anesthesia (submucosal infiltration and/or nerve block) during a dental procedure.</p>
<p>Failure Mode: Name confusion</p>	<p>Causes (could be multiple)</p>	<p>Rationale</p>
<p>Septocaine (Articaine with Epinephrine) Injection</p> <p>Septocaine is the reference listed drug product that has been referenced under 505(b)(2) for Capacaine.</p>	<p>Orthographic</p> <p>1) ‘Sep-’ and ‘Cap-’ looks similar and have downstroke with letter ‘p’ in same position</p> <p>2) Last syllable, -caine, in each name are identical</p> <p>Capacaine and Carbocaine are similar products with identical indication, identical strength, and identical dose. Although not bioequivalent by FDA standards, the products will likely be used as therapeutically interchangeable by dentists in their offices and clinics.</p>	<p>Usual Dose of Septocaine/Capacaine (identical):</p> <p>Doses up to 7 mg/kg (0.175 mL/kg), based on articaine component, are used for local anesthesia (submucosal infiltration and/or nerve block) during a dental procedure.</p> <p>Argument:</p> <p>Septocaine and Capacaine can look similar when scripted. Both products share the same indication for use (local dental anesthesia), share identical strengths, and have identical overlapping doses that can increase the potential for confusion. Both Septocaine and Capacaine will be stored and administered in dental offices and dental surgical suites and administered to the same population by the same practitioners (dentists and oral surgeons). Consequently, a medication error may not be readily detected. However, should a medication error occur, it would likely not be clinically significant due to the shared indication, strength, and doses of the two products.</p>

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/s/

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